52481

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

SEARCH REQUEST FORM

Requestor's Name: Rebecca Cook CM1 2B07 Serial Number: 09/865,125

Date: 10/6/01 Phone: 308 4724 Art Unit: 1614

Rupew 2501

Search Topic:

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevant citations, authors keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevant claim(s).

Thomas Tobin - inv

5/24/01 date

Please provide structures of compounds of claims 2 + 13 + known uses.

Please search methods of claims 21 + 30.

Thank you
Rebecca

POINT OF CONTACT:
BARB O'BRYEN
TECH. INFORMATION SPECIALIST
STIC CM1 12C14 308-4291

STAFF USE ONLY

Date completed: 10-15-01
Searcher: BOB
Terminal time: 141
Elapsed time: prep 40
CPU time:
Total time:
Number of Searches:
Number of Databases:

Search Site
- ____ STIC
- ____ CM-1
- ____ Pre-S

Type of Search
- ____ N.A. Sequence
- ____ A.A. Sequence
- ____ Structure
- X Bibliographic

Vendors
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- 615 STN
- ____ Dialog
- ____ APS
- ____ Geninfo
- ____ SDC
- ____ DARC/Questel
- WWW - PDR Other

What is claimed is:

1. A veterinary composition, useful for providing a rapid onset and long lasting analgesia and sedation in an animal, comprising a pharmaceutically effective amount of a guanidine derivative.

2. The composition of claim 1, wherein the guanidine derivative is selected from the group consisting of guanabenz, guanabenz acetate, guanoxabenz, clonidine, guanacline, guanadrel, guanazodine, guanethidine, guanfacine and guanochlor, guanoxan and chlonidine.

3. The composition of claim 1, wherein the guanadine derivative is guanabenz, guanabenz acetate or pharmaceutically acceptable derivatives thereof.

4. The composition of claim 1, further comprising a pharmaceutically acceptable carrier.

5. The composition of claim 1, wherein the composition is adapted for oral administration.

6. The composition of claim 1, wherein the composition is adapted for intravenous administration.

7. The composition of claim 1, wherein the composition is adapted for intravmuscular administration.

8. The composition of claim 1, wherein the animal is selected from the group

consisting of equine, canine, feline, bovine, caprine, porcine and ovine.

9. The composition of claim 1, wherein the animal is an equine.

10. The composition of claim 1, wherein the animal is a standing animal.

11. The composition of claim 1, wherein the analgesia and sedation are rapidly reversible.

12. The composition of claim 11, wherein the analgesia and sedation are reversed via administration of a pharmaceutically effective amount of an α adrenergic antagonist.

13. The composition of claim 12 wherein the α adrenergic antagonist is selected from the group consisting of yohimbine, rauwolscine, idazoxan and atepamezole.

14. The composition of claim 1, wherein the pharmaceutically effective amount is between about 0.05 mg/kg and about 0.50 mg/kg.

15. The composition of claim 14, wherein the pharmaceutically effective amount is about 0.25 mg/kg.

16. The composition of claim 1, wherein the guanidine derivative is guanabenz acetate or a pharmaceutically acceptable derivative thereof and the pharmaceutically effective amount is between about 0.05 mg/kg and about 0.50 mg/kg.

17. The composition of claim 1, wherein the guanidine derivative is guanabenz acetate or a pharmaceutically acceptable derivative thereof and the pharmaceutically effective amount is about 0.25 mg/kg.

18. The composition of claim 1, wherein the guanidine derivative is an α - adrenergic agonist.

19. The composition of claim 1 in a unit dosage form.

20. A method of inducing rapid onset and long lasting sedation and analgesia in an animal, comprising administering to the animal a pharmaceutically effective amount of a composition comprised of a guanidine derivative.

21.

22. The method of claim 20, wherein the guanadine derivative is guanabenz acetate or pharmaceutically acceptable derivatives thereof.

23. The method of claim 20, wherein the administration is oral.

24. The method of claim 20, wherein the administration is intravenous.

25. The method of claim 20, wherein the administration is intramuscular.

26. The method of claim 20, wherein the animal is selected from the group consisting of equine, canine, feline, bovine, caprine, porcine and ovine.

27. The method of claim 20, wherein the animal is an equine.

28. The method of claim 20 wherein the rapid onset sedation and analgesia is induced in a standing animal .

29.

30.

31. The method of claim 20, wherein the pharmaceutically effective amount of the guanidine derivative is between about 0.05 mg/kg and about 0.50 mg/kg.

32. The method of claim 20, wherein the pharmaceutically effective amount of the guanidine derivative is about 0.25 mg/kg.

33. The method of claim 20, wherein the guanidine derivative is guanabenz acetate or a pharmaceutically acceptable derivative thereof and the pharmaceutically effective amount is between about 0.05 mg/kg and about 0.50 mg/kg.

34. The method of claim 20, wherein the guanidine derivative is guanabenz acetate or a pharmaceutically acceptable derivative thereof and the pharmaceutically effective amount is about 0.25 mg/kg.

35. The method of claim 20, wherein the guanidine derivative is an α - adrenergic agonist.

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STRUCTURE FILE UPDATES: 14 OCT 2001 HIGHEST RN 362009-74-3
DICTIONARY FILE UPDATES: 14 OCT 2001 HIGHEST RN 362009-74-3

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

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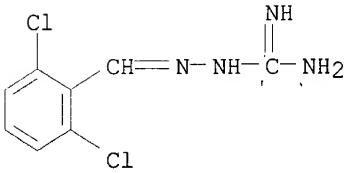
Crossover limits have been increased. See HELP CROSSOVER see HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 5051-62-7 REGISTRY
CN Hydrazinecarboximidamide, 2-[(2,6-dichlorophenyl)methylene]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Guanidine, [(2,6-dichlorobenzylidene)amino]- (7CI, 8CI)
OTHER NAMES:
CN **Guanabenz**
CN N-(2,6-Dichlorobenzylidene)-N'-amidinohydrazine
CN Wy 8678
CN [(2,6-Dichlorobenzylidene)amino]guanidine
FS 3D CONCORD
MF C8 H8 Cl2 N4
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CHEMCATS, CHEMLIST, DDFU, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, PHAR, PROMT, SYNTHLINE, TOXLINE, TOXLIT, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



514634

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1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS

RN 23256-50-0 REGISTRY
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OTHER CA INDEX NAMES:
CN Guanidine, [(2,6-dichlorobenzylidene)amino]-, monoacetate (8CI)
OTHER NAMES:
CN 1-(2,6-Dichlorobenzylideneamino)guanidine acetate
CN BR 750
CN **Guanabenz acetate**
CN Wy 8678 acetate
CN Wytensin
CN [(2,6-Dichlorobenzylidene)amino]guanidine acetate
MF C8 H8 Cl2 N4 . C2 H4 O2
LC STN Files: ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CHEMCATS, CHEMLIST, CIN, CSCHEM, DIOGENES, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, PHAR, PROMT, RTECS*, SYNTHLINE, TOXLINE, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

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CRN 5051-62-7
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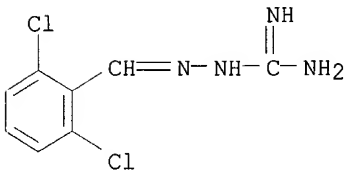

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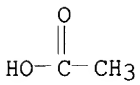

79 REFERENCES IN FILE CA (1967 TO DATE)
80 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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Crossover limits have been increased.  See HELP CROSSOVER see
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http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf


L25  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2001 ACS
RN   55-65-2  REGISTRY
CN   Guanidine, [2-(hexahydro-1(2H)-azocinyl)ethyl]- (8CI, 9CI)  (CA INDEX
     NAME)
OTHER CA INDEX NAMES:
CN   Azocine, guanidine deriv.
OTHER NAMES:
CN   2-(1'-Azacyclooctyl)ethylguanidine
CN   2-(1-N,N-Heptamethyleneimino)ethylguanidine
CN   Abapresin
CN   Azocine, 1-[[2-(aminoiminomethyl)amino]ethyl]octahydro-
CN   Dopom
CN   Eutensol
CN   Guanethidine
CN   Ismelin
CN   N-(2-Perhydroazocin-1-ylethyl)guanidine
CN   [2-(Octahydro-1-azocinyl)ethyl]guanidine
FS   3D CONCORD
MF   C10 H22 N4
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
       BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CHEMLIST, CIN, DDFU, DIOGENES,
       DRUGU, EMBASE, HSDB*, IPA, MEDLINE, MRCK*, NIOSHTIC, PROMT, RTECS*,
       SPECINFO, TOXLINE, TOXLIT, USAN, USPATFULL
         (*File contains numerically searchable property data).
     Other Sources:   EINECS**, WHO
         (**Enter CHEMLIST File for up-to-date regulatory information)
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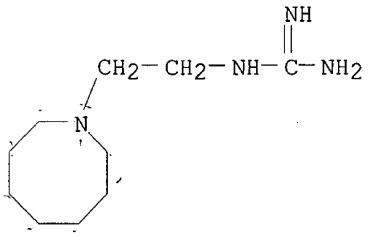

514/183

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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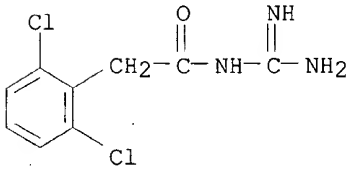
Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

L26 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 29110-47-2 REGISTRY
CN Benzeneacetamide, N-(aminoiminomethyl)-2,6-dichloro- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Acetamide, N-amidino-2-(2,6-dichlorophenyl)- (8CI)
OTHER NAMES:
CN Guanfacin
CN **Guanfacine**
CN Guanfascine
CN Guarfacine
CN N-Amidino-2-(2,6-dichlorophenyl)acetamide
CN [(2,6-Dichlorophenyl)acetyl]guanidine
FS 3D CONCORD
MF C9 H9 Cl2 N3 O
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, CHEMLIST, CIN, DDFU, DIOGENES, DRUGPAT, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, PHAR, PROMT, SYNTHLINE, TOXLINE, TOXLIT, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



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338 REFERENCES IN FILE CA (1967 TO DATE)
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338 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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HELP CROSSOVER for details.

Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf



L53  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2001 ACS
RN   146-48-5  REGISTRY
CN   Yohimban-16-carboxylic acid, 17-hydroxy-, methyl ester,
     (16.alpha.,17.alpha.)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Benz[g]indolo[2,3-a]quinolizine, yohimban-16-carboxylic acid deriv.
CN   Yohimban-16.alpha.-carboxylic acid, 17.alpha.-hydroxy-, methyl ester (8CI)
CN   Yohimbol-16.alpha.-carboxylic acid, methyl ester (6CI)
OTHER NAMES:
CN   (+)-Yohimbine
CN   Aphrodine
CN   Aphrosol
CN   Corynine
CN   Quebrachin
CN   Quebrachine
CN   trans-Quinolizidine yohimbine
CN   Yohimbic acid methyl ester
CN   Yohimbin
CN   Yohimbine
FS   STEREOSEARCH
DR   54725-25-6, 80925-02-6
MF   C21 H26 N2 O3
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
       BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS,
       CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DETHERM*, DIOGENES, DRUGU,
       EMBASE, HODOC*, IFICDB, IFIUDB, IPA, MEDLINE, MRCK*, NAPRALERT,
       NIOSHTIC, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXLINE, TOXLIT,
       USPATFULL, VETU
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Absolute stereochemistry.
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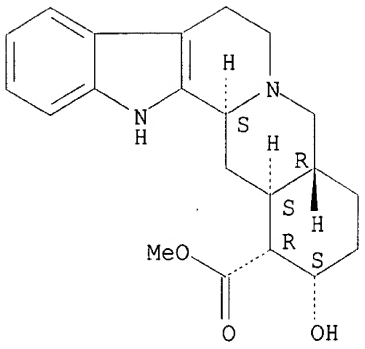

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1889 REFERENCES IN FILE CAPLUS (1967 TO DATE)
3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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L54 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 131-03-3 REGISTRY
CN Yohimban-16-carboxylic acid, 17-hydroxy-, methyl ester, (16.beta.,17.alpha.,20.alpha.)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 20.alpha.-Yohimban-16.beta.-carboxylic acid, 17.alpha.-hydroxy-, methyl ester (8CI)
CN Benz[g]indolo[2,3-a]quinolizine, yohimban-16-carboxylic acid deriv.
CN **Rauwolscine (6CI, 7CI)**
OTHER NAMES:
CN .alpha.-Yohimbine
CN Corynanthidine
CN Isoyohimbine
CN meso-Yohimbine
CN Mesoyohimbine
FS STEREOSEARCH
DR 1358-49-2, 1392-02-5
MF C21 H26 N2 O3
CI COM
LC STN Files: ADISNEWS, AGRICOLA, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CHEMLIST, DDFU, DRUGU, EMBASE, IPA, MRCK*, NAPRALERT, RTECS*, SPECINFO, TOXLINE, TOXLIT, USPATFULL
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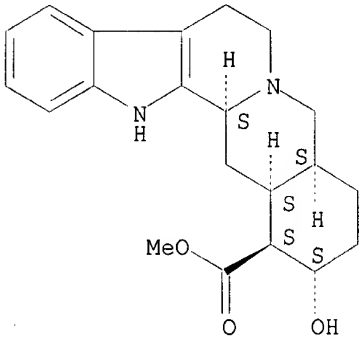
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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28 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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STRUCTURE FILE UPDATES: 14 OCT 2001 HIGHEST RN 362009-74-3
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L55 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 79944-58-4 REGISTRY
CN 1H-Imidazole, 2-(2,3-dihydro-1,4-benzodioxin-2-yl)-4,5-dihydro- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,4-Benzodioxin, 1H-imidazole deriv.
CN 2-Imidazoline, 2-(1,4-benzodioxan-2-yl)- (6CI)
OTHER NAMES:
CN (.+-.)-Idazoxan
CN dl-Idazoxan
CN **Idazoxan**
CN Racemic idazoxan
FS 3D CONCORD
DR 84720-37-6
MF C11 H12 N2 O2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CBNB, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IFICDB, IFIUDB, IPA, MEDLINE, MRCK*, PHAR, PROMT, RTECS*, SYNTHLINE, TOXLINE, TOXLIT, USAN, USPATFULL, VETU
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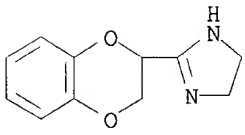
Other Sources: WHO



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1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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FILE 'REGISTRY' ENTERED AT 11:59:24 ON 15 OCT 2001
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HELP CROSSOVER for details.

Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf


L3   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2001 ACS
RN   24047-25-4  REGISTRY
CN   Hydrazinecarboximidamide, 2-[(2,6-dichlorophenyl)methylene]-N-hydroxy-
     (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Guanidine, 1-[(2,6-dichlorobenzylidene)amino]-3-hydroxy- (8CI)
OTHER NAMES:
CN   1-(2,6-Dichlorobenzylideneamino)-3-hydroxyguanidine
CN   Guanoxabenz
CN   Hydroxyguanabenz
FS   3D CONCORD
MF   C8 H8 Cl2 N4 O
CI   COM
LC   STN Files:   ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, DDFU,
       DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, MEDLINE, MRCK*, PHAR, TOXLINE,
       TOXLIT, USAN, USPATFULL
         (*File contains numerically searchable property data)
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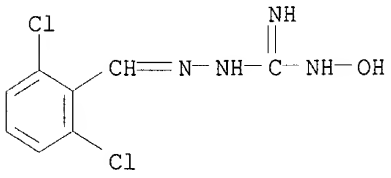


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

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L4           18 SEA FILE=MEDLINE ABB=ON  L3
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L5            27 SEA FILE=CAPLUS ABB=ON  L3
L6             2 SEA FILE=CAPLUS ABB=ON  L5(L)USES/RL


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FILE 'CAPLUS' ENTERED AT 12:02:16 ON 15 OCT 2001
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PROCESSING COMPLETED FOR L4
PROCESSING COMPLETED FOR L6
L7            19 DUP REM L4 L6 (1 DUPLICATE REMOVED)
                 ANSWERS '1-18' FROM FILE MEDLINE
                 ANSWER '19' FROM FILE CAPLUS

=> d ibib ab 1-18; d ibib ab hitrn 19

L7   ANSWER 1 OF 19     MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:    1998016239     MEDLINE
DOCUMENT NUMBER:     98016239   PubMed ID: 9351903
TITLE:               Formation of guanoxabenz from guanabenz in human liver. A
                     new metabolic marker for CYP1A2.
AUTHOR:              Clement B; Demesmaeker M
CORPORATE SOURCE:    Pharmazeutisches Institut, Christian-Albrechts-Universitat
                     Kiel.
SOURCE:              DRUG METABOLISM AND DISPOSITION, (1997 Nov) 25 (11)
                     1266-71.
                     Journal code: EBR; 9421550. ISSN: 0090-9556.
PUB. COUNTRY:        United States
                     Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         199802
ENTRY DATE:          Entered STN: 19980224
                     Last Updated on STN: 19980224
                     Entered Medline: 19980209
AB   The in vitro N-hydroxylation of guanabenz as well as the corresponding
     N-dehydroxylation of guanoxabenz has been previously detected in
     biotransformation studies with microsomal fractions of different species
     including human hepatic microsomes. Furthermore, the N-hydroxylation of
     guanabenz was found to be catalyzed by enriched cytochrome P450 (P450)
     fractions in reconstituted systems. Strong correlations between
     7-ethoxyresorufin O-deethylation (r = 0. 96; p < 0.001), caffeine
     N-demethylation (r = 0.92; p < 0.001), respectively, and guanabenz
     N-hydroxylation activities were demonstrated in 10 human liver microsomal
     preparations. Studies with microsomes from human B-lymphoblastoid cell
     lines expressing human cytochrome P450 enzymes proved that CYP1A2 is the
     major isozyme responsible for this metabolic pathway. Further, P450
     isozymes did not show any detectable conversion rates. The reaction was
     inhibited in presence of the potent CYP1A2 inhibitors alpha-naphthoflavone
     (7, 8-benzoflavone) and furafylline. The N-reduction of guanoxabenz to
     guanabenz exhibits a significant correlation to the benzamidoxime
     N-reduction after incubation with 10 human liver microsomal preparations
     (r = 0.97; p < 0.001). The formation of benzamidine from benzamidoxime was
     described previously to be catalyzed by the benzamidoxime reductase. These
     results suggest that the guanabenz N-hydroxylation is mediated via CYP1A2,
     whereas the corresponding guanoxabenz N-reduction is catalyzed by an
     enzyme system composed of cytochrome b5, NADH cytochrome b5-reductase, and
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benzamidoxime reductase. The high affinity of guanabenz to CYP1A2 and the distinct selectivity of this P450 isozyme toward guanabenz confirms the in vitro guanabenz N-hydroxylation to be a suitable metabolic marker for CYP1A2 in biotransformation studies.

L7 ANSWER 2 OF 19 MEDLINE
ACCESSION NUMBER: 2000025586 MEDLINE
DOCUMENT NUMBER: 20025586 PubMed ID: 10556947
TITLE: Cardioprotective effects of N-hydroxyguanidine PR5 in myocardial ischaemia and reperfusion in rats.
AUTHOR: Veveris M; Dambrova M; Cirule H; Meirena D; Kalvinsh I; Wikberg J E
CORPORATE SOURCE: Department of Medicinal Chemistry, Latvian Institute of Organic Synthesis, Riga, Latvia.
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (1999 Nov) 128 (5) 1089-97.
Journal code: B00; 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000124

AB 1. The potential for the N-hydroxyguanidine compound PR5 (N-(3, 4-dimethoxy-2-chlorobenzylideneamino)-N'-hydroxyguanidine) as a cardioprotective agent in heart ischaemia and reperfusion injury was investigated using rat models. 2. Administration of 1-10 mg kg-1 of PR5 5 min before 10 min of left coronary artery occlusion, followed by 20 min reperfusion, strongly inhibited reperfusion burst of arrhythmias and markedly improved the survival of the animals (e.g. ventricular fibrillation incidence 93 vs 43% (P<0.05); mortality 47 vs 0% (P<0.05), for controls and for 3 mg kg-1 of PR5, respectively). 3. Administration of 3 mg kg-1 of PR5 1 min before reperfusion to rats subjected to 10 min occlusion, 20 min reperfusion was most effective in reducing arrhythmias and decreasing mortality (43 vs 0%, P<0.05), but effects were also seen when PR5 was administered 0, 1 and 5 min after start of reperfusion. 4. Coronary occlusion/reperfusion (10 - 20 min) increased malondialdehyde (MDA) of rat hearts (0.88+/-0.13 for sham vs 1.45+/-0.12 nmol mg-1 protein for ischaemic; P<0.05). In rats where 3 mg kg-1 PR5 were administered 1 min before reperfusion the increase was attenuated (MDA being 1.04+/-0.12; P<0.05 vs ischaemic). 5. PR5 caused a substantial reduction of the infarction size in rats subjected to 180 min left coronary artery occlusion, followed by 120 min of reperfusion; the necrotic zone being 326+/-32 mg for controls vs 137+/-21 mg for animals treated with 3x3 mg kg-1 of PR5 (P<0.01). 6. PR5 reduced the elevation of the ST-segment of the ECGs, as well as caused pronounced attenuation of the rapid blood pressure drop seen at the start of reperfusion following coronary artery occlusion. 7 We conclude that the N-hydroxyguanidine PR5 provides remarkable protection against ischaemia and reperfusion induced myocardial necrosis and life-threatening arrhythmias. These effects of PR5 are discussed in relation to a recently discovered ability of N-hydroxyguanidines to function as electron acceptors at the xanthine oxidase enzyme.

L7 ANSWER 3 OF 19 MEDLINE
ACCESSION NUMBER: 1999017307 MEDLINE
DOCUMENT NUMBER: 99017307 PubMed ID: 9802321
TITLE: Characterization of the enzymatic activity for biphasic competition by guanoxabenz (1-(2,6-dichlorobenzylidene-amino)-3-hydroxyguanidine) at alpha2-adrenoceptors. II. Description of a xanthine-dependent enzymatic activity in

spleen cytosol.
AUTHOR: Dambrova M; Uhlen S; Welch C J; Prusis P; Wikberg J E
CORPORATE SOURCE: Department of Pharmaceutical Biosciences, Uppsala University, Sweden.
SOURCE: BIOCHEMICAL PHARMACOLOGY, (1998 Nov 1) 56 (9) 1121-8. Journal code: 9Z4; 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981117

AB The mechanism for formation of high affinity binding of guanoxabenz (1-(2,6-dichlorobenzylidene-amino)-3-hydroxyguanidine) to alpha2-adrenoceptors by the rat spleen cytosol was studied. We report here that the spleen cytosolic fraction mediated the reduction of guanoxabenz to guanabenz (1-(2,6-dichlorobenzylidene-amino)-3-guanidine), the latter having an almost 100-fold higher affinity for rat alpha2A-adrenoceptors than guanoxabenz itself. The reaction product could be separated by high-performance liquid chromatography and its identity as guanabenz confirmed by nuclear magnetic resonance. The spleen cytosolic activity could be separated into high and low molecular weight components, the high molecular weight component requiring low molecular weight factors for maximal activity. Xanthine oxidase seems to be the most likely candidate responsible for the activity, as the guanoxabenz-reducing activity of the high molecular weight component could be sustained by exogenously applied xanthine, while it was potently blocked by allopurinol. The conversion of guanoxabenz by the cytosolic activity was also quite potently blocked by DWO1, 1-(3,4-dimethoxybenzylideneamino)3-hydroxyguanidine, a hydroxyguanidine analogue to guanoxabenz.

L7 ANSWER 4 OF 19 MEDLINE
ACCESSION NUMBER: 1999017306 MEDLINE
DOCUMENT NUMBER: 99017306 PubMed ID: 9802320
TITLE: Characterization of the enzymatic activity for biphasic competition by guanoxabenz (1-(2,6-dichlorobenzylidene-amino)-3-hydroxyguanidine) at alpha2-adrenoceptors. I. Description of an enzymatic activity in spleen membranes.
AUTHOR: Uhlen S; Dambrova M; Tiger G; Oliver D W; Wikberg J E
CORPORATE SOURCE: Department of Pharmaceutical Biosciences, Uppsala University, Sweden.
SOURCE: BIOCHEMICAL PHARMACOLOGY, (1998 Nov 1) 56 (9) 1111-9. Journal code: 9Z4; 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981117

AB The mechanism for formation of high-affinity binding of 1-(2,6-dichlorobenzylidene-amino)-3-hydroxyguanidine (guanoxabenz) to alpha2-adrenoceptors was studied in particulate fractions from the rat spleen. The proportion of apparent high versus low-affinity alpha2-adrenoceptor binding sites increased with increasing incubation time and was also augmented by Mg2+ ions. The formation of high-affinity guanoxabenz binding seemed to be inhibited by a series of N-hydroxyguanidine analogs to guanoxabenz, as well as by a series of metabolic inhibitors that included allopurinol, 1-chloro-2,4-dinitrobenzene, 5,5'-dithiobis-(2-nitrobenzoic acid), cibacron blue,

phenyl-p-benzoquinone, didox, and trimidox. The formation of guanoxabenz high-affinity binding was also inhibited in a time- and concentration-dependent fashion by preincubating the membranes with the LW03 N-hydroxyguanidine analogue of guanoxabenz. Moreover, when the spleen membranes were extensively washed for 30 min with buffers at 25 degrees, the guanoxabenz high-affinity binding disappeared. However, when these washed membranes were supplemented with xanthine, the apparent affinity of guanoxabenz increased four to five-fold. Taken together, all data were compatible with the theory that the formation of high-affinity binding was dependent on the generation of a guanoxabenz metabolite that showed an approximate 100-fold greater affinity for the alpha2-adrenoceptors than guanoxabenz itself. Because the most potent blocker of the formation of high-affinity binding was allopurinol (apart from some N-hydroxyguanidine analogs to guanoxabenz) and since the activity could be restored with xanthine, a likely candidate responsible for the metabolic activation is xanthine oxidase.

L7 ANSWER 5 OF 19 MEDLINE
ACCESSION NUMBER: 1999013461 MEDLINE
DOCUMENT NUMBER: 99013461 PubMed ID: 9799117
TITLE: Identification of an N-hydroxyguanidine reducing activity of xanthine oxidase.
AUTHOR: Dambrova M; Uhlen S; Welch C J; Wikberg J E
CORPORATE SOURCE: Department of Pharmaceutical Biosciences, Uppsala University, Sweden.
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (1998 Oct 1) 257 (1) 178-84.
Journal code: EMZ; 0107600. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981110

AB A guanoxabenz [1-(2,6-dichlorobenzylideneamino)-3-hydroxyguanidine; an N-hydroxyguanidine] reducing enzymatic activity of rat spleen cytosol was investigated. By means of protein purification and N-terminal amino acid sequencing, the reducing activity was shown to reside in xanthine oxidase. The action of the enzyme on guanoxabenz resulted in the formation of guanabenz [1-(2,6-dichlorobenzylidene-amino)-3-guanidine]; the product formation could be monitored by HPLC and its identity was confirmed by NMR analysis. The reduction of guanoxabenz required xanthine or NADH as reducing substrates, while the process could be blocked by allopurinol, a selective inhibitor of xanthine oxidase. By using bovine milk xanthine oxidase, the guanoxabenz reducing activity of the enzyme was also verified. We conclude that guanoxabenz is a novel electron acceptor structure for xanthine oxidase.

L7 ANSWER 6 OF 19 MEDLINE
ACCESSION NUMBER: 1999038317 MEDLINE
DOCUMENT NUMBER: 99038317 PubMed ID: 9820876
TITLE: Characterization of guanoxabenz reducing activity in rat brain.
AUTHOR: Dambrova M; Uhlen S; Wikberg J E
CORPORATE SOURCE: Department of Pharmaceutical Biosciences, Uppsala University, Sweden.
SOURCE: PHARMACOLOGY AND TOXICOLOGY, (1998 Oct) 83 (4) 158-63.
Journal code: PHT; 8702180. ISSN: 0901-9928.
PUB. COUNTRY: Denmark
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 19990209
Entered Medline: 19990122

AB Guanoxabenz (1-(2,6-dichlorobenzylidene-amino)-3-hydroxyguanidine) and guanabenz (1-(2,6-dichlorobenzylidene-amino)-3-guanidine) are both known as centrally active antihypertensive drugs. We have previously shown that enzymatic activity in the rat spleen can induce N-reduction of guanoxabenz, leading to high affinity alpha 2-adrenoceptor binding, due to the formation of the alpha 2-adrenoceptor active drug, guanabenz. The spleen activity appears to reside in xanthine oxidase as it is activated by xanthine and blocked by allopurinol. We report that high affinity guanoxabenz binding is also induced in rat brain membranes after addition of NADH or NADPH cofactors. However, the brain process was clearly different from that of the spleen, as the formation of high affinity binding in the brain was not blocked by allopurinol. Moreover the NADH/NADPH activated mechanism of the brain membranes was not blocked by carbon monoxide and SKF525A, thus the activity appears not to reside in cytochrome P450 enzymes. Instead the activity was blocked by menadione and dicumarol. We conclude that the rat cerebral cortex contains an enzymatic activity that may activate guanoxabenz leading to formation of a metabolite showing high affinity for alpha 2-adrenoceptors. We also conclude that the rat brain activity is clearly distinct from that of the rat spleen.

L7 ANSWER 7 OF 19 MEDLINE
ACCESSION NUMBER: 96428708 MEDLINE
DOCUMENT NUMBER: 96428708 PubMed ID: 8831810
TITLE: Microsomal catalyzed N-hydroxylation of guanabenz and reduction of the N-hydroxylated metabolite: characterization of the two reactions and genotoxic potential of guanoxabenz.
AUTHOR: Clement B; Demesmaeker M; Linne S
CORPORATE SOURCE: Pharmazeutisches Institut, Christian-Albrechts-Universitat Kiel, Germany.
SOURCE: CHEMICAL RESEARCH IN TOXICOLOGY, (1996 Jun) 9 (4) 682-8.
Journal code: A5X; 8807448. ISSN: 0893-228X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961119

AB The N-reduction of the centrally acting alpha 2-adrenoreceptor agonist guanoxabenz (Benzerial), an N-hydroxyamidinohydrazone, to the amidinohydrazone guanabenz (Wytensin, Hipten, Rexitene) by microsomal fractions from rabbits, pigs and humans has been detected in vitro. The conversion rates with rabbit microsomal fractions were markedly slower than those in the cases of fractions from humans and pigs. It was also possible to demonstrate the N-oxidation of guanabenz to guanoxabenz by the use of microsomal fractions from rabbits, pigs, and humans. Furthermore, the oxidation was also observed in reconstituted systems in the presence of enriched cytochrome P450 fractions, purified isoenzyme P450 2C3, and heterologously expressed P450 2C3 of the subforms 6 beta H and 6 beta L. The analyses were performed with a newly developed HPLC technique and were confirmed by LC-MS methods. The kinetic parameters determined for the metabolic cycle (bioreversible reactions) are indicative of a predominance of the reduction of guanoxabenz to guanabenz in vivo. Accordingly, guanoxabenz in part constitutes a prodrug of guanabenz. Examination of guanabenz and guanoxabenz for mutagenicity by means of the Ames test

revealed that guanoxabenz has pronounced mutagenic effects in the strains TA 98 and TA 1537. Guanabenz did not exhibit mutagenicity so that the N-reduction of guanoxabenz has significance in terms of detoxification.

L7 ANSWER 8 OF 19 MEDLINE
ACCESSION NUMBER: 96145048 MEDLINE
DOCUMENT NUMBER: 96145048 PubMed ID: 8572879
TITLE: [Evidence for two alpha 2B-adrenoreceptor isoforms in the renal cortex of salt-sensitive and salt resistant Sabra rats. Effect of salt loading].
Distinction de deux isofromes de recepteurs alpha 2B-adrenergiques dans le cortex renal des rats Sabra sensibles et resistants au sel. Effet d'une surcharge en sel.
AUTHOR: Le Jossec M; Cloix J F; Dausse J P
CORPORATE SOURCE: Service de biochimie de Paris-Ouest, UFR biomedicale des Saints-Peres, Paris.
SOURCE: ARCHIVES DES MALADIES DU COEUR ET DES VAISSEAUX, (1995 Aug) 88 (8) 1229-32.
Journal code: 7SM; 0406011. ISSN: 0003-9683.
PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960315
Last Updated on STN: 19960315
Entered Medline: 19960304

AB alpha 2-adrenoceptors are involved in various renal functions regulating blood pressure. They were classified in subtypes whom genes were identified in both humans and rats. In rat renal cortex it was evidenced that the alpha 2B isoform is predominant. This result was confirmed in Sabra rats. However, the renal cortex alpha 2B density is higher in salt-sensitive (SBH) than in salt-resistant (SBN) Sabra rats. alpha 2B-adrenoceptors were recently subclassified in two pharmacologically distinct subtypes exhibiting high and low affinity for guanoxabenz and respectively called alpha 2B1 and alpha 2B2. We studied sodium loading effect on alpha 2B1 and alpha 2B2 distribution in Sabra rat renal cortex using competition experiments between [3H]-yohimbine and guanoxabenz. The rats were submitted to normal (0.2%) or high sodium diet (8%) for six weeks. Under normal diet, proportion alpha 2B1 and alpha 2B2 was similar in SBH and SBN. Nevertheless, their respective densities were significantly higher in SBH as compared to SBN (alpha 2B1: 90.6 +/- 4.1 vs 57.4 +/- 2.5 fmoles/mg prot, $p < 0.0001$; $n = 5$; alpha 2B2: 102.7 +/- 4.0 vs 66.4 +/- 4.6 fmoles/mg prot; $p < 0.0001$; $n = 5$). Under high sodium diet the distribution of these two isoforms was altered. The densities of alpha 2B1 were decreased by 27.0 +/- 5.9% in SBH (68.0 +/- 4.0 fmoles/mg prot; $p < 0.0001$, $n = 5$) and by 47.3 +/- 7.4% for SBN (29.2 +/- 3.1 fmoles/mg prot; $p < 0.0001$; $n = 5$). Conversely, the densities of alpha 2B2 were increased by 28.3 +/- 5.4% in SBH (131.1 +/- 9.5 fmoles/mg prot; $p < 0.001$; $n = 5$) and by 75.0 +/- 17% in SBN (123.2 +/- 9.1 fmoles/mg prot; $p < 0.0001$; $n = 5$). In conclusion, alpha 2B1- and alpha 2B2-adrenoceptor subtypes are found in renal cortex of both SBH and SBN. Our data demonstrated an equal distribution of these two isoforms between SBH and SBN under normal salt diet. This distribution is largely altered, especially in SBN, by the high sodium diet. From these modifications might result differential renal responses to activation of alpha 2B-adrenoceptors between SBH and SBN, and consequently responsible for normal or high blood pressure after high sodium diet.

L7 ANSWER 9 OF 19 MEDLINE
ACCESSION NUMBER: 94328114 MEDLINE
DOCUMENT NUMBER: 94328114 PubMed ID: 7914222

[redacted]

TITLE: Alpha 2-adrenoceptor subtypes identified by [3H]RX821002 binding in the human brain: the agonist guanoxabenz does not discriminate different forms of the predominant alpha 2A subtype.
AUTHOR: Sastre M; Garcia-Sevilla J A
CORPORATE SOURCE: Department of Fundamental Biology and Health Sciences, University of the Balearic Islands, Palma de Mallorca, Spain.
SOURCE: JOURNAL OF NEUROCHEMISTRY, (1994 Sep) 63 (3) 1077-85.
Journal code: JAV; 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199409
ENTRY DATE: Entered STN: 19940914
Last Updated on STN: 19950206
Entered Medline: 19940908

AB Competition [3H]RX821002 ([3H]2-methoxyidazoxan) binding experiments with alpha 2-adrenoceptor subtype-specific antagonists--BRL 44408 (alpha 2A selectively), ARC 239 (alpha 2B selective), and others--were performed to delineate through rigorous computer modeling receptor subtypes in the postmortem human brain. In the hippocampus, hypothalamus, cerebellum, and brainstem the whole population of alpha 2-adrenoceptors appears to belong to the alpha 2A subtype (100%; Bmax = 34-90 fmol/mg of protein). In the frontal cortex, the predominant receptor was the alpha 2A subtype (87%; Bmax = 53 fmol/mg of protein), although a small population of the alpha 2B/C subtype (13%; Bmax = 8 fmol/mg of protein) was also detected. In the caudate nucleus, a mixed population of alpha 2A (64%; Bmax = 9 fmol/mg of protein) and alpha 2B/C (36%; Bmax = 5 fmol/mg of protein) subtypes was detected. In the cortex and caudate and in the presence of ARC 239 (to mask the alpha 2B/C-adrenoceptors), competition experiments with the agonist guanoxabenz clearly modeled the high- and low-affinity states of the alpha 2A subtype. In the presence of ARC 239 and the GTP analogue guanylyl-5'-imidodiphosphate together with NaCl and EDTA (to eliminate the high-affinity alpha 2A-adrenoceptor) guanoxabenz only recognized the low-affinity alpha 2A-adrenoceptor. The results indicate that in the human brain the predominant alpha 2-adrenoceptor is of the alpha 2A subtype and that this functionally relevant receptor subtypes is not heterogeneous in nature.

L7 ANSWER 10 OF 19 MEDLINE
ACCESSION NUMBER: 92182865 MEDLINE
DOCUMENT NUMBER: 92182865 PubMed ID: 1665747
TITLE: Delineation of three pharmacological subtypes of alpha 2-adrenoceptor in the rat kidney.
AUTHOR: Uhlen S; Wikberg J E
CORPORATE SOURCE: Department of Pharmacology, Umea University, Sweden.
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (1991 Nov) 104 (3) 657-64.
Journal code: B00; 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 19920424
Last Updated on STN: 19920424
Entered Medline: 19920416

AB 1. Simultaneous computer modelling of plain and ARC 239- and guanoxabenz-masked [3H]-RX821002 saturation curves, plain ARC 239 and guanoxabenz competition curves as well as ARC 239-masked guanoxabenz competition curves revealed that the drugs bound to three alpha 2-adrenoceptor subtypes in the rat kidney with grossly differing

selectivities. These alpha 2-adrenoceptor subtypes were termed alpha 2 A, alpha 2B1 and alpha 2B2. The order of affinities for [3H]-RX821002 for the adrenoceptor sites was alpha 2A greater than alpha 2B1 greater than alpha 2B2, the KdS being 0.62 +/- 0.05, 2.52 +/- 0.11 and 6.74 +/- 1.21 nM, respectively. The order of affinities for ARC 239 was alpha 2B1 greater than alpha 2B2 much greater than alpha 2A with KdS 4.78 +/- 1.04, 28.8 +/- 4.1 and 1460 +/- 270 nM, respectively. For guanoxabenz the order of affinities was alpha 2A greater than alpha 2B1 much greater than alpha 2B2 with KdS 99.7 +/- 15.1, 508 +/- 135 and 25,400 +/- 2400 nM, respectively. 2. Binding constants for 14 compounds for the three rat kidney alpha 2-adrenoceptor subtypes were determined by the simultaneous computer modelling of plain and ARC 239- and guanoxabenz-masked drug competition curves, plain ARC 239 and guanoxabenz competition curves as well as ARC 239-masked guanoxabenz competition curves. Of the 14 compounds tested, oxymetazoline and guanfacine were found to bind with low affinities to both of the alpha 2B1- and alpha 2B2-adrenoceptor but with high affinity to the alpha 2A-adrenoceptor.(ABSTRACT TRUNCATED AT 250 WORDS)

L7 ANSWER 11 OF 19 MEDLINE
ACCESSION NUMBER: 86049044 MEDLINE
DOCUMENT NUMBER: 86049044 PubMed ID: 2865924
TITLE: [Use of presynaptic alpha-mimetics for withdrawal in heroin addicts].
Utilisation des alpha-mimetiques pre-synaptiques dans le sevrage des heroinomanes.
AUTHOR: Gorceix A; Dugarin J; Pommier F
SOURCE: ANNALES DE MEDECINE INTERNE, (1985) 136 (5) 389-92.
Journal code: 5FZ; 0171744. ISSN: 0003-410X.
PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198512
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19970203
Entered Medline: 19851213
AB We report the results of two studies carried out in the Drug Addiction Unit of Fernand-Widal hospital, on the use of presynaptic alpha-mimetic drugs in the treatment of heroin addicts. The authors briefly recall the mode of action of these drugs, and then describe the methodology of these two studies of Guanoxabenz and Guanfacine; characteristics of this group, outcome of therapy, mode of prescription, side effects. The results are analysed and compared with the usual methods of treatment using synthetic opiates.

L7 ANSWER 12 OF 19 MEDLINE
ACCESSION NUMBER: 83297988 MEDLINE
DOCUMENT NUMBER: 83297988 PubMed ID: 6136932
TITLE: Neuropharmacological studies in rodents on the action of RX 781094, a new selective alpha 2-adrenoceptor antagonist.
AUTHOR: Dettmar P W; Lynn A G; Tulloch I F
SOURCE: NEUROPHARMACOLOGY, (1983 Jun) 22 (6) 729-37.
Journal code: NZB; 0236217. ISSN: 0028-3908.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198310
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19831021
AB Several neuropharmacological effects of RX 781094, a new selective alpha 2-adrenoceptor antagonist, have been investigated in rodents. In rats, RX

[redacted]

781094 (0.1-1.0 mg kg-1, i.v.) produced a rapid dose-related reversal of cortical EEG synchronisation and behavioural sedation, induced by clonidine or the more selective alpha 2-adrenoceptor agonist, guanoxabenz. The alpha 2-adrenoceptor antagonists yohimbine and mianserin were also effective in blocking guanoxabenz-induced EEG synchronisation but had a lower potency than did RX 781094. In specificity experiments, RX 781094 (1.0 mg kg-1, i.v.) failed to antagonise the EEG synchronisation and pronounced behavioural sedation induced by the CNS depressant sodium pentobarbitone (15 mg kg-1, i.v.). In mice, pretreatment (i.v. or p.o.) with RX 781094 inhibited in a dose-dependent way both guanoxabenz-induced behavioural hypoactivity and clonidine-induced hypothermia. By itself, RX 781094 had no effect on the temperature of normal mice. In sleep-waking studies in rats, RX 781094 (0.1 and 1.0 mg kg-1, i.v.) had no measurable stimulant or depressant effect on the CNS, in contrast to (+)-amphetamine (1.0 mg kg-1, i.v.) which elicited marked CNS stimulation. These results support the conclusion that RX 781094 is a potent antagonist at central alpha 2-adrenoceptors.

L7 ANSWER 13 OF 19 MEDLINE
ACCESSION NUMBER: 83179473 MEDLINE
DOCUMENT NUMBER: 83179473 PubMed ID: 6132641
TITLE: alpha 2-Adrenoceptor agonists induced mydriasis in the rat by an action within the central nervous system.
AUTHOR: Berridge T L; Gadie B; Roach A G; Tulloch I F
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (1983 Mar) 78 (3) 507-15. Journal code: B00; 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198306
ENTRY DATE: Entered STN: 19900318
Last Updated on STN: 19970203
Entered Medline: 19830610

AB 1 The effects of intravenous administration of the selective alpha 2-adrenoceptor agonists clonidine, UK 14,304 and guanoxabenz on rat pupil diameter were investigated. 2 In rats anaesthetized with pentobarbitone, each agonist produced a marked dose-related increase in pupil diameter; the rank order of potency was: clonidine greater than UK 14,304 greater than guanoxabenz. 3 Pretreatment with the selective alpha 2-adrenoceptor antagonist, RX 781094 (0.5 mg/kg, i.v.), produced a parallel 30-40 fold shift to the right of the dose-pupil dilator response curves for the three agonists. Yohimbine (1.5 mg/kg, i.v.) produced about a 10 fold rightward shift of the dose-response curve for guanoxabenz. In contrast, the alpha 1-selective antagonist, prazosin (0.5 mg/kg, i.v.), failed to affect the dose-response relation for guanoxabenz. 4 Several antagonists of varying selectivities towards alpha 1- and alpha 2-adrenoceptors were tested for their ability to reverse the maximal mydriasis induced by guanoxabenz (0.3 mg/kg, i.v.). The rank order of potency of the antagonists producing a 50% reversal of this effect was: RX 781094 greater than yohimbine greater than piperoxan = rauwolscine greater than mianserin greater than RS 21361. Neither corynanthine nor prazosin reversed the guanoxabenz-induced mydriasis. 5 Topical application of RX 781094 (0.1 to 3% w/v solutions) onto one eye produced a slow reversal of guanoxabenz-induced mydriasis; the time course and degree of reversal were virtually the same in both eyes. 6 Intracerebroventricular administration of RX 781094 (1.25-15 micrograms total dose) caused a rapid dose-related reversal of the maximal mydriasis induced by guanoxabenz (0.3 mg/kg, i.v.). 7 Guanoxabenz (0.3 and 1.0 mg/kg, i.v.) did not produce any dilation of the physostigmine-constricted undamaged pupil of the pithed rat. Intravenous adrenaline was found to produce a small mydriatic effect, while atropine completely antagonized the effects of physostigmine in this preparation. 8 These results indicate that alpha 2-adrenoceptor agonists induce mydriasis in

the rat through a central alpha 2-adrenoceptor mechanism. However, the site of action within the central nervous system remains to be determined.

L7 ANSWER 14 OF 19 MEDLINE
ACCESSION NUMBER: 84035723 MEDLINE
DOCUMENT NUMBER: 84035723 PubMed ID: 6138427
TITLE: Sleeping times evoked by alpha adrenoceptor agonists in two-day-old chicks: an experimental model to evaluate full and partial agonists at central alpha-2 adrenoceptors.
AUTHOR: Roach A G; Doxey J C; Strachan D A; Cavero I
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1983 Nov) 227 (2) 421-8.
Journal code: JP3; 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198312
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19950206
Entered Medline: 19831217

AB The ability of a series of alpha adrenoceptor agonists to induce a sleep-like state (as measured by the time interval between the loss and regaining of the righting reflex) has been assessed in 2-day-old chicks in order to understand their pharmacological profile better. Guanabenz, guanoxabenz, UK-14,304, guanfacine and xylazine produced dose-related increases in sleeping time, the highest dose of these agonists causing the chicks to sleep for over 120 min. In contrast, the dose-response curves to tiamenidine and clonidine were flatter and bell-shaped with maxima of 30 and 60 min, respectively. The effects of all these compounds were antagonized by idazoxan (RX781094) and yohimbine (two selective alpha-2 adrenoceptor antagonists) but were moderately enhanced or unaffected by prazosin (a selective alpha-1 adrenoceptor antagonist) confirming that the state of arousal in chicks can be depressed by stimulation of alpha-2 adrenoceptors. In particular, idazoxan displaced significantly the guanoxabenz dose-response curve to the right without affecting its slope and apparent maximum and blocked the sleep induced by clonidine. However, idazoxan failed to affect the sleep evoked by ethanol, etorphine or pentobarbital. Naloxone antagonized the effects of etorphine but not those of guanoxabenz, ethanol or pentobarbital. The relatively selective alpha-1 adrenoceptor agonist, cirazoline, given in doses up to 20 mg/kg i.m., produced in chicks behavioral manifestations suggestive of enhanced arousal.(ABSTRACT TRUNCATED AT 250 WORDS)

L7 ANSWER 15 OF 19 MEDLINE
ACCESSION NUMBER: 83254557 MEDLINE
DOCUMENT NUMBER: 83254557 PubMed ID: 6870157
TITLE: [Treatment of acute pulmonary edema with injectable guanoxabenz. Apropos of 26 cases].
Traitement de l'oedeme aigu du poumon par le guanoxabenz injectable. A propos de 26 observations.
AUTHOR: Tardy C; Savelli J; Errera J; Puech P
SOURCE: ANNALES DE CARDIOLOGIE ET D ANGEIOLOGIE, (1983 Jan-Feb) 32 (1) 69-72.
Journal code: 502; 0142167. ISSN: 0003-3928.
PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198308
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19900319
Entered Medline: 19830826

Searched by Barb O'Bryen, STIC 308-4191

[redacted]

L7 ANSWER 16 OF 19 MEDLINE
ACCESSION NUMBER: 82040428 MEDLINE
DOCUMENT NUMBER: 82040428 PubMed ID: 7027519
TITLE: [A clinical trial of guanoxabenz: a hypotensive agent with central and hypertensive action (author's transl)].
Essai clinique du guanoxabenz, un hypotenseur a action centrale et peripherique. Etude preliminaire.
AUTHOR: Ledoux F; Welsch M; Steimer C; Schwartz J
SOURCE: THERAPIE, (1981 Mar-Apr) 36 (2) 187-91.
Journal code: VQ6; 0420544. ISSN: 0040-5957.
PUB. COUNTRY: France
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198112
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19900316
Entered Medline: 19811215

L7 ANSWER 17 OF 19 MEDLINE
ACCESSION NUMBER: 81253729 MEDLINE
DOCUMENT NUMBER: 81253729 PubMed ID: 7258704
TITLE: [Single dose of thiopental or fentanyl. Hemodynamic effects after treatment by an anti-hypertensive drug: guanoxabenz (author's transl)].
Effets hemodynamiques d'une injection unique de thiopental ou de fentanyl apres le traitement par un anti-hypertenseur: le guanoxabenz.
AUTHOR: Delhumeau A; Leboulanger J; Chapillon M; Cavellat M
SOURCE: ANESTHESIE, ANALGESIE, REANIMATION, (1981) 38 (3-4) 105-12.
Journal code: 4RU; 0404017. ISSN: 0003-3014.
PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198109
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 20000303
Entered Medline: 19810915

AB The hemodynamic effects of a single dose of fentanyl (4 micrograms/kg) and of thiopental (5 mg/kg) were studied on cranial trauma patients who have hypertension and who are ventilated at constant volume and frequency. At first the results were collected without an hypertensive treatment, in the second time the same results were collected after the injection of an anti-hypertensive drug (guanoxabenz 70 micrograms/kg). The results showed that in two series the modification in the measured parameters was not statistically significant; the used drugs produced little change in the hemodynamic profile: a) Even with insignificant, we noted that the injection of fentanyl after an anti-hypertensive drug caused a smaller change in the blood pressure and cardiac index then was seen in untreated subjects. b) With thiopental treated subjects, the arterial pressure is not decreased because of the increased systemic resistances, at the same time changes in cardiac index are essentially identical whether or not the subject was treated with guanoxabenz. The results therefore tend to show that the anti-hypertensive treatment can be continued without any interruption by a surgical operation.

L7 ANSWER 18 OF 19 MEDLINE
ACCESSION NUMBER: 81158205 MEDLINE
DOCUMENT NUMBER: 81158205 PubMed ID: 7212391
TITLE: [Estimation of guanoxabenz in biological fluids (author's

transl)].
Dosage du guanoxabenz dans les liquides biologiques.
AUTHOR: Hoffelt J; Bourdon R
SOURCE: ANNALES DE BIOLOGIE CLINIQUE, (1980) 38 (6) 351-4.
Journal code: 4ZS; 2984690R. ISSN: 0003-3898.
PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198105
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19900316
Entered Medline: 19810521

AB A molecule sensitive to light, to variations in temperature and pH, guanoxabenz hydrochloride cannot be estimated in biological fluids according to classical technics. The authors propose an analytical method based, during the extraction phase, on the formation of a copper complex extractable in organic medium and in the true phase of measurement, on the transformation, by hydrochloric acid hydrolysis in dichloro-2-6-benzaldehyde, estimated by gas phase chromatography with detection by capture of electrons. The sensitivity and the specificity of the technic authorise its use in pharmacokinetic studies in man.

L7 ANSWER 19 OF 19 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:385500 CAPLUS
DOCUMENT NUMBER: 129:49654
TITLE: Use of hydroxyguanidines for treatment or prevention of an ischemic disease
INVENTOR(S): Wikberg, Jarl; Prusis, Peteris; Dambrova, Maija; Uhlen, Staffan
PATENT ASSIGNEE(S): Wapharm AB, Swed.; Wikberg, Jarl; Prusis, Peteris; Dambrova, Maija; Uhlen, Staffan
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9823267	A1	19980604	WO 1997-SE1969	19971121
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9851430	A1	19980622	AU 1998-51430	19971121
EP 1007025	A1	20000614	EP 1997-946211	19971121
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, LV, FI				
JP 2001505209	T2	20010417	JP 1998-524603	19971121

PRIORITY APPLN. INFO.: SE 1996-4348 A 19961126
WO 1997-SE1969 W 19971121
OTHER SOURCE(S): MARPAT 129:49654

AB Hydroxyguanidines are useful for the manuf. of a medicament for treatment or prevention of an ischemic disease condition including an ischemic

condition caused by surgery or other therapy and being assocd. with the prodn. of oxygen-derived radicals, the disease condition being a xanthine oxidase/xanthine dehydrogenase-mediated ischemic condition selected from heart infarction, angina pectoris, cerebrovascular infarction, circulatory shock, etc. Preferred hydroxyguanidines are carbimino hydroxyguanidines, in particular aryl carbimino hydroxyguanidines. Also disclosed are corresponding methods of treatment, including extracorporeal treatment of organs, and a no. of hydroxyguanidines and their prepn. The presence of 100 .mu.M guanoxabenz resulted in about 60% redn. of superoxide formation by xanthine oxidase in the presence of oxygen.

IT **24047-25-4P**, Guanoxabenz
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process);
USES (Uses)
(hydroxyguanidines for treatment or prevention of ischemic diseases)

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DICTIONARY FILE UPDATES:  14 OCT 2001  HIGHEST RN 362009-74-3

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for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf


L8   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2001 ACS
RN   1463-28-1  REGISTRY
CN   Guanidine, [2-(3,6-dihydro-4-methyl-1(2H)-pyridinyl)ethyl]- (9CI)  (CA
     INDEX NAME)
OTHER CA INDEX NAMES:
CN   Guanidine, [2-(3,6-dihydro-4-methyl-1(2H)-pyridyl)ethyl]- (7CI, 8CI)
OTHER NAMES:
CN   Guanacline
CN   [2-(3,6-Dihydro-4-methyl-1(2H)-pyridyl)ethyl]guanidine
FS   3D CONCORD
MF   C9 H18 N4
CI   COM
LC   STN Files:   BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, DDFU,
       DRUGU, EMBASE, MEDLINE, MRCK*, TOXLINE, TOXLIT, USAN
         (*File contains numerically searchable property data)
     Other Sources:   WHO
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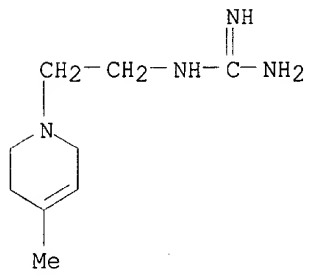

514/315

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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

             11 REFERENCES IN FILE CA (1967 TO DATE)
             11 REFERENCES IN FILE CAPLUS (1967 TO DATE)
              2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)
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=> d que l9; d que l10
L8             1 SEA FILE=REGISTRY ABB=ON  GUANACLINE/CN
L9             2 SEA FILE=MEDLINE ABB=ON  L8



L8             1 SEA FILE=REGISTRY ABB=ON  GUANACLINE/CN
L10           11 SEA FILE=CAPLUS ABB=ON  L8


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PROCESSING COMPLETED FOR L10
L12           11 DUP REM L9 L10 (2 DUPLICATES REMOVED)
                 ANSWERS '1-2' FROM FILE MEDLINE
                 ANSWERS '3-11' FROM FILE CAPLUS

=> d ibib ab 1-2; d ibib ab hitrn 3-11

L12  ANSWER 1 OF 11    MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:    87155210     MEDLINE
DOCUMENT NUMBER:     87155210   PubMed ID: 3827214
TITLE:               Sympathetic neuronal destruction in macaque monkeys by
                     guanethidine and guanacline.
AUTHOR:              Palmatier M A; Schmidt R E; Plurad S B; Johnson E M Jr
CONTRACT NUMBER:     AM19645 (NIADDK)
                     GM07805-A04 (NIGMS)
                     HL20604 (NHLBI)
                     +
SOURCE:              ANNALS OF NEUROLOGY, (1987 Jan) 21 (1) 46-52.
                     Journal code: 6AE; 7707449. ISSN: 0364-5134.
PUB. COUNTRY:        United States
                     Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         198704
ENTRY DATE:          Entered STN: 19900303
                     Last Updated on STN: 19970203
                     Entered Medline: 19870415
AB   To determine whether the peripheral sympathetic neurons of subhuman
     primates are destroyed by guanacline treatment, we treated Macaca
     fasicularis with 2 or 20 mg/kg of guanethidine, guanacline, or the
     saturated analog of guanacline (SAG) 5 times per week for 4 or 12 weeks.
     All monkeys given 20 mg/kg of guanethidine, guanacline, or SAG showed a
     marked loss of neurons in the ganglia of the peripheral sympathetic
     nervous system. Treatment of macaques with 2 mg/kg of the guanidinium
     compounds resulted in patches of small-cell infiltrate, slight neuronal
     loss, and degenerative alterations in the sympathetic ganglia. Neuronal
     alterations in sympathetic ganglia of all treated monkeys were accompanied
     by a prominent heterogeneous infiltrate of mononuclear cells arranged
     primarily in a perivascular distribution and extending into the ganglionic
     neuropil. Peripheral sensory ganglia were unaffected. These histological
     findings are similar to those described in the guanethidine-induced
     immune-mediated sympathectomy, which has been extensively studied in the
     rat.

L12  ANSWER 2 OF 11    MEDLINE                          DUPLICATE 2
```

ACCESSION NUMBER: 87027472 MEDLINE
DOCUMENT NUMBER: 87027472 PubMed ID: 3768685
TITLE: Species and structural specificity of the lipopigment accumulation and neuronal destruction induced by N-(2-guanidinoethyl)-4-methyl-1,2,5,6-tetrahydropyridine (guanacline).
AUTHOR: Johnson E M Jr; Palmatier M A; Rydel R E; Manning P T
CONTRACT NUMBER: 5-T32-GM07805 (NIGMS)
HL20604 (NHLBI)
SOURCE: BRAIN RESEARCH, (1986 Sep 24) 383 (1-2) 100-9.
Journal code: B5L; 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198612
ENTRY DATE: Entered STN: 19900302
Last Updated on STN: 19970203
Entered Medline: 19861210

AB Guanacline, a guanidinium adrenergic neuron blocking agent similar to guanethidine, was studied clinically and experimentally during the late 1960s. Like guanethidine, it has been reported to produce sympathetic neuronal destruction in rats. Unlike guanethidine, it has been reported to produce irreversible sympathetic deficits in man and to produce fluorescent lipopigment in rat sympathetic neurons. Guanacline and its derivative in which the double bond of the tetrahydropyridine ring is reduced (saturated analog of guanacline, SAG) were prepared. Several species were treated chronically with varying doses of guanethidine, guanacline or SAG; the superior cervical ganglia were examined light microscopically for neuronal destruction and for osmiophilic fluorescent lipopigment accumulation. All 3 drugs produced rapid neuronal destruction in rats accompanied by massive small-cell infiltration. In striking contrast, treatment for many weeks with doses up to 100 mg/kg/day produced no small-cell infiltration or apparent neuronal destruction in mice or guinea pigs. The neuronal destruction produced by guanacline and SAG in the rat, like that caused by guanethidine, was prevented by immunosuppression or gamma-irradiation, indicating that all 3 agents produce neuronal destruction in rats by an immune-mediated mechanism. Thus, the ability of the drug to produce sympathectomy is species specific but not drug specific. The opposite was found with respect to fluorescent lipopigment accumulation. Guanacline, but not guanethidine or SAG, produced fluorescent lipopigment in all species examined. Therefore, the double bond of the tetrahydropyridine ring plays a critical role in the production of the fluorescent lipopigment.(ABSTRACT TRUNCATED AT 250 WORDS)

L12 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:823 CAPLUS
DOCUMENT NUMBER: 118:823
TITLE: Adrenergic agonists and antagonists for treatment of sympathetically maintained pain
INVENTOR(S): Campbell, James N.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9214453	A1	19920903	WO 1992-US1543	19920226
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
EP 573581	A1	19931215	EP 1992-907852	19920226
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE				
JP 06507392	T2	19940825	JP 1992-5073	19920226
US 5447947	A	19950905	US 1992-905496	19920625
PRIORITY APPLN. INFO.:			US 1991-661554	19910226
			US 1991-747635	19910820
			US 1990-485156	19900226
			WO 1992-US1543	19920226

OTHER SOURCE(S): MARPAT 118:823

AB Sympathetically maintained pain (SMP) is treated topically by administering an .alpha.-1-adrenergic antagonist, .alpha.-2-adrenergic agonist, or other drug that depletes or blocks synthesis of sympathetic norepinephrine, i.e., sympatholytic agents. Examples are given showing that topical application of clonidine reduced mech. and cold hyperalgesia at the site of drug administration in patients with SMP.

IT **1463-28-1**
RL: BIOL (Biological study)
(sympathetically maintained pain treatment by topical administration of)

L12 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1990:458878 CAPLUS
DOCUMENT NUMBER: 113:58878
TITLE: In vivo intracerebral microdialysis studies in rats of MPP+ (1-methyl-4-phenylpyridinium) analogs and related charged species
AUTHOR(S): Rollema, Hans; Johnson, E. Anne; Booth, Raymond G.; Caldera, Patricia; Lampen, Peter; Youngster, Stephen K.; Trevor, Anthony J.; Naiman, Noreen; Castagnoli, Neal, Jr.
CORPORATE SOURCE: Dep. Med. Chem., Univ. Cent. Pharm., Groningen, 9713 AW, Neth.
SOURCE: J. Med. Chem. (1990), 33(8), 2221-30
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 113:58878

AB The in vivo dopaminergic neurotoxic properties of 45 analogs of MPTP and MPP+ and related compds. were examd. by an intrastriatal microdialysis assay in conscious rats. MPP+-like toxicity, as evidenced by the irreversible effects on dopamine (DA) release and enhancement of lactate formation, was obsd. with a variety of structural types although no compd. was more toxic than MPP+. The following global structure-toxicity relationships could be derived: (1) Only permanently charged compds. showed neurotoxic effects. (2) With the exception of amino groups, hydrophilic substituents abolished toxicity. (3) Activity was enhanced by lipophilic groups although increased steric bulk around the N atom tended to decrease activity. (4) Nonarom., quaternary systems (methiodide of MPTP, guanidinium derivs.) were only weakly toxic. (5) Certain bi- and tricyclic systems, including putative metabolites of potential endogenous MPTP-like compds., were weakly toxic. The lack of toxic effects following perfusions with DA itself confirmed that MPTP dopaminergic neurotoxicity is not likely to be mediated by the MPP+-induced release of DA. With some interesting exceptions, these in vivo data correlate reasonably well with in vitro data on the nerve terminal uptake properties and the inhibitory effects on mitochondrial respiration of these compds.

IT **1463-28-1**, Guanacline
RL: RCT (Reactant)

(dopaminergic neurotoxicity of)

L12 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1987:451727 CAPLUS
DOCUMENT NUMBER: 107:51727
TITLE: The effect of guanacline treatment on peripheral sympathetic neurons
AUTHOR(S): Palmatier, Margaret Ann
CORPORATE SOURCE: Washington Univ., St. Louis, MO, USA
SOURCE: (1986) 157 pp. Avail.: Univ. Microfilms Int., Order No. DA8704941
From: Diss. Abstr. Int. B 1987, 47(11), 4428
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable
IT **1463-28-1**, Guanacline
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(peripheral sympathetic neuron response to)

L12 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1978:436703 CAPLUS
DOCUMENT NUMBER: 89:36703
TITLE: Cytotoxicity of a series of guanidine derivatives
AUTHOR(S): Juul, Per
CORPORATE SOURCE: Dep. Pharmacol., R. Danish Sch. Pharm., Copenhagen, Den.
SOURCE: Alfred Benzon Symp. (1977), 10(Drug Des. Adverse React.), 63-76
CODEN: ABSYB2
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Guanethidine (I) [55-65-2] and guanacline [**1463-28-1**] administered to rats induced chromatolysis of the nerve cells accompanied by an infiltration of small cells, but guanochlor [5001-32-1], guanisoquin [154-73-4], guanoctine [3658-25-1], and guancydine [1113-10-6] had no significant effects.
IT **1463-28-1**
RL: PRP (Properties)
(toxicity of, to nerve)

L12 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1971:97841 CAPLUS
DOCUMENT NUMBER: 74:97841
TITLE: Prolonged hypotension and ultrastructural changes in sympathetic neurones following guanacline treatment
AUTHOR(S): Burnstock, Geoffery; Doyle, A. E.; Gannon, B. J.; Gerkens, J. F.; Iwayama, Takashi; Mashford, M. L.
CORPORATE SOURCE: Dep. Zool., Austin Hosp., Parkville, Aust.
SOURCE: Eur. J. Pharmacol. (1971), 13(2), 175-87
CODEN: EJPHAZ
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of guanacline (I) on systemic blood pressure, catechol amine levels, fluorescent histochemistry and ultrastructure of sympathetic neurons were compared with those of guanethidine (II) in rats both during and after chronic treatments. The systemic blood pressure fell steadily for the first 9-14 weeks in both I- and II-treated animals. Following cessation of drugs, the blood pressure of II-treated animals rose rapidly to normal levels, while the rise was slow in I-treated animals. In contrast to II, I (5 mg/kg/day, i.p.) caused ultrastructural changes in sympathetic ganglion cells, characterized by a massive deposition of lipoprotein granules in the neurons. These granules were still present 12

weeks after cessation of the treatment.
IT **1463-28-1**
RL: BIOL (Biological study)
(hypotension from, lipoproteins in nerves in)

L12 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1971:96605 CAPLUS
DOCUMENT NUMBER: 74:96605
TITLE: Sympathetic innervation of vascular smooth muscle in normal and hypertensive animals
AUTHOR(S): Burnstock, Geoffery; Gannon, B. J.; Iwayama, Takashi
CORPORATE SOURCE: Dep. Zool., Univ. Melbourne, Parkville, Aust.
SOURCE: Circ. Res., Suppl. (1970), 27(2), II, 5-21
CODEN: CIRSAF
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The nerves supplying most blood vessels are confined to an adventitial-medial plexus. A model of the vascular autonomic neuromuscular junction is proposed which explains the activation of muscle fibers on the intimal side of the media in terms of intermuscle fiber spread of activity. Species variation in sympathetic innervation of different vessels is described, including the demonstration of nerve fibers within the medial muscle coat in some large arteries and veins. A preliminary account of the ultrastructural pathol. of sympathetic vasomotor nerves in sheep with renal hypertension is included; an increase in intra-axonal vesicles and in the size and d. of their granular cores as compared with control nerves is demonstrated. The mechanism of action of some antihypertensive drugs, including guanethidine, guanacline, reserpine, and 6-hydroxydopamine, is examd. with the electron microscope. Chronic treatment of rats with guanacline produces a marked deposition of lipoprotein granules in sympathetic nerves, an effect which is long-lasting and perhaps irreversible.
IT **1463-28-1**
RL: BIOL (Biological study)
(nerves of blood vessels in response to)

L12 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1970:65300 CAPLUS
DOCUMENT NUMBER: 72:65300
TITLE: Persistent postural hypotension due to guanacline
AUTHOR(S): Dawborn, J. K.; Doyle, A. E.; Ebringer, A.; Howqua, June; Jerums, G.; Johnston, Colin I.; Mashford, M. L.; Parkin, J. D.
CORPORATE SOURCE: Austin Hosp., Univ. Melbourne, Heidelberg, Aust.
SOURCE: Pharmacol. Clin. (1969), 2(1), 1-5
CODEN: PHCLAL
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Case histories of 5 patients are presented who developed severe postural hypotension after being treated with guanacline. The postural hypotension did not develop until treatment had been given for 3-4 months and persisted following withdrawal of guanacline for 12-15 months. It is suggested that this drug causes irreversible depletion of noradrenaline stores in adrenergic nerve terminals in some patients.
IT **1463-28-1**
RL: BIOL (Biological study)
(hypotension from)

L12 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1967:1532 CAPLUS
DOCUMENT NUMBER: 66:1532
TITLE: Clinical and experimental studies with a new hypotensive agent: dichlorophenylaminoimidazoline

AUTHOR(S): Bock, Klaus D.; Heimsoth, Volker; Merguet, P.; Schoenermark, J.
CORPORATE SOURCE: Univ. Muenster, Muenster, Ger.
SOURCE: Dtsch. Med. Wochenschr. (1966), 91(40), 1761-70
CODEN: DMWOAX
DOCUMENT TYPE: Journal
LANGUAGE: German

AB When assessed on 51 hypertensive patients and 18 healthy normotensive subjects, the title compd. (I) exhibited a satisfactory antihypertensive action corresponding somewhat to that of .alpha.-methyldopa (II) in intensity and, as in the case of other antihypertensive agents, was enhanced in activity by saluretic agents; combinations of I with II, cyclazenine, guanethidine, and reserpine were well tolerated. Daily therapeutic doses lay between 0.225 and 0.35 mg., given orally in 3-4 batches/day, and between 0.15 and 0.30 mg. given intravenously (i.v.); i.v. administration elicited an immediate drop in blood pressure, whereas a blood-pressure decrease set in after .apprx.30 min. with oral doses; the effective period of action amounted to 3-6 hrs. on these doses. The major untoward side effects observed were dryness of the mouth and sedative action (in 42 and 41 patients, resp.); these and other side effects discussed were essentially moderate and minimal. The possible mechanism of action of I was elucidated.

IT **1463-28-1**
RL: BIOL (Biological study)
(hypertension treatment with catapresan and)

L12 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1967:452695 CAPLUS
DOCUMENT NUMBER: 67:52695
TITLE: Evaluation of drugs acting at ganglionic and post ganglionic sites of the adrenergic nerve
AUTHOR(S): Stoepel, Kurt; Kroneberg, Guenther
CORPORATE SOURCE: Inst. Pharmacol, Farbenfabriken Bayer A.G., Wuppertal-Elberfeld, Ger.
SOURCE: Methods Drug Eval., Proc. Int. Symp. (1966), Meeting Date 1965, 174-82
CODEN: 16LKAC
DOCUMENT TYPE: Conference
LANGUAGE: English

AB An investigation of newly synthesized guanidine derivs. was performed to differentiate ganglionic and postaganglonic adrenergic-blocking activities. Methods used included pre- and postganglionic stimulation of the nictitating membrane and peripheral vagus stimulation in the cat, antinicotinic potency in the isolated guinea pig ileum and atrium, comparison of nictitating membrane response to postganglionic stimulation with pressor response to splanchnic stimulation, and catechol amine content of the rat heart. Results from all these methods led to the conclusion that the most promising adrenergic neuron-blocking agents for clin. trials in hypertensive patients may be those which have only weak ganglionic-blocking properties and whose chief site of action is at the postganglionic fiber. The catechol amine-depleting activity appears to be more important than the brethyliumlike activity (output of noradrenaline from adrenergic nerve fibers can be inhibited without changing the total catechol amine content), esp. in regard to the onset and duration of hypotensive action.

IT **1463-28-1**
RL: BIOL (Biological study)
(as nerve center blocking agent)

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=> fil reg; d ide l13
FILE 'REGISTRY' ENTERED AT 12:06:28 ON 15 OCT 2001
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L13  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2001 ACS
RN   40580-59-4  REGISTRY
CN   Guanidine, (1,4-dioxaspiro[4.5]dec-2-ylmethyl)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   1,4-Dioxaspiro[4.5]decane, guanidine deriv.
OTHER NAMES:
CN   Guanadrel
CN   N-(1,4-Dioxaspiro[4.5]dec-2-ylmethyl)guanidine
FS   3D CONCORD
MF   C10 H19 N3 O2
CI   COM
LC   STN Files:   ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS, CA, CANCERLIT,
       CAPLUS, CASREACT, DDFU, DRUGPAT, DRUGU, EMBASE, HSDB*, IPA, MEDLINE,
       MRCK*, PHAR, PROMT, TOXLINE, TOXLIT, USAN, USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:   WHO
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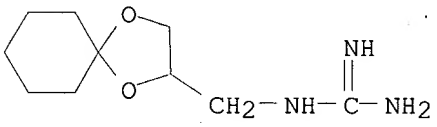

5/14/462

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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

             16 REFERENCES IN FILE CA (1967 TO DATE)
             16 REFERENCES IN FILE CAPLUS (1967 TO DATE)


=> d que l18; d que l16; dup rem l18,l16
L13            1 SEA FILE=REGISTRY ABB=ON  GUANADREL/CN
L14           25 SEA FILE=MEDLINE ABB=ON  L13
L17        13266 SEA FILE=MEDLINE ABB=ON  GUANIDINES/CT
L18           17 SEA FILE=MEDLINE ABB=ON  L17/MAJ AND L14
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L13           1 SEA FILE=REGISTRY ABB=ON  GUANADREL/CN
L15          16 SEA FILE=CAPLUS ABB=ON  L13
L16           4 SEA FILE=CAPLUS ABB=ON  L15(L)USES/RL


FILE 'MEDLINE' ENTERED AT 12:08:23 ON 15 OCT 2001

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PROCESSING COMPLETED FOR L16
L19          20 DUP REM L18 L16 (1 DUPLICATE REMOVED)
                ANSWERS '1-17' FROM FILE MEDLINE
                ANSWERS '18-20' FROM FILE CAPLUS

=> d ibib ab 1-17; d ibib ab hitrn 18-20

L19  ANSWER 1 OF 20     MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:   83299542     MEDLINE
DOCUMENT NUMBER:    83299542   PubMed ID: 6351026
TITLE:              Guanadrel sulfate: a postganglionic sympathetic inhibitor
                    for the treatment of mild to moderate hypertension.
AUTHOR:             Palmer J D; Nugent C A
SOURCE:             PHARMACOTHERAPY, (1983 Jul-Aug) 3 (4) 220-9.
                    Journal code: PAR; 8111305. ISSN: 0277-0008.
PUB. COUNTRY:       United States
                    (CLINICAL TRIAL)
                    Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        198310
ENTRY DATE:         Entered STN: 19900319
                    Last Updated on STN: 19970203
                    Entered Medline: 19831028

L19  ANSWER 2 OF 20     MEDLINE
ACCESSION NUMBER:   94262764     MEDLINE
DOCUMENT NUMBER:    94262764   PubMed ID: 8203510
TITLE:              Arterial alpha-adrenergic responsiveness is decreased and
                    SNS activity is increased in older humans.
AUTHOR:             Hogikyan R V; Supiano M A
CORPORATE SOURCE:   Department of Internal Medicine, University of Michigan,
                    Ann Arbor.
CONTRACT NUMBER:    AG-00433 (NIA)
                    AG-08802 (NIA)
                    RR-00042 (NCRR)
                    +
SOURCE:             AMERICAN JOURNAL OF PHYSIOLOGY, (1994 May) 266 (5 Pt 1)
                    E717-24.
                    Journal code: 3U8; 0370511. ISSN: 0002-9513.
PUB. COUNTRY:       United States
                    Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        199407
ENTRY DATE:         Entered STN: 19940714
                    Last Updated on STN: 19940714
                    Entered Medline: 19940707
AB   We tested the hypotheses that 1) there is an age-associated decrease in
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arterial alpha-adrenergic responsiveness and 2) there is upregulation of this response during suppression of sympathetic nervous system (SNS) activity. We measured forearm blood flow (FABF) by plethysmography during brachial artery infusions of the alpha-adrenergic agonist norepinephrine (NE) and the nonadrenergic agonist angiotensin II (ANG II) in 15 young and 14 older healthy human subjects. Among the old (O) relative to the young (Y) we identified greater plasma NE levels (Y: 1.29 +/- 0.07 nM vs. O: 2.14 +/- 0.17 nM; P = 0.0001); a decrease in NE-mediated reduction in FABF [analysis of variance (ANOVA) P = 0.04]; and, in contrast, no difference in ANG II-mediated reduction in FABF (ANOVA P = 0.43). In the nine older subjects studied during guanadrel (G) to suppress SNS activity, we identified decreased plasma NE levels [placebo (P): 2.11 +/- 0.24 nM vs. G: 1.09 +/- 0.09 nM; P = 0.002], increased NE-mediated FABF response (ANOVA P = 0.01), and no difference in FABF response to ANG II (ANOVA: P = 0.69) compared with P. We conclude that there is appropriate desensitization of arterial alpha-adrenergic responsiveness among the older relative to the young subjects that is specific for the alpha-adrenergic system. Among the older subjects there is homologous upregulation of this response when SNS activity is suppressed.

L19 ANSWER 3 OF 20 MEDLINE
ACCESSION NUMBER: 93232265 MEDLINE
DOCUMENT NUMBER: 93232265 PubMed ID: 8473492
TITLE: Homologous upregulation of human arterial alpha-adrenergic responses by guanadrel.
AUTHOR: Hogikyan R V; Supiano M A
CORPORATE SOURCE: Department of Internal Medicine, University of Michigan, Ann Arbor.
CONTRACT NUMBER: AG-00433 (NIA)
AG-08808 (NIA)
RR-00042 (NCRR)
+
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1993 Apr) 91 (4) 1429-35.
Journal code: HS7; 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199305
ENTRY DATE: Entered STN: 19930604
Last Updated on STN: 19970203
Entered Medline: 19930514

AB The purpose of this study was to test the hypothesis that there is homologous upregulation of arterial alpha-adrenergic responsiveness during suppression of sympathetic nervous system (SNS) activity in humans. 10 subjects (19-28 yr) were studied during placebo and when SNS activity was suppressed by guanadrel. Changes in forearm blood flow (FABF) mediated by the intraarterial infusion of norepinephrine (NE), angiotensin II (AII), and phentolamine were measured by plethysmography. During guanadrel compared with placebo, plasma NE levels (1.28 +/- 0.09-0.85 +/- 0.06 nM; P = 0.0001) and the extra vascular NE release rate derived from [3H]NE kinetics were lower (7.1 +/- 0.7-4.0 +/- 0.2 nmol/min per m2; P = 0.0004), suggesting suppression of SNS activity. During guanadrel, there was increased sensitivity in the FABF response to NE (analysis of variance P = 0.03). In contrast, there was no difference in the FABF response to AII (analysis of variance P = 0.81), suggesting that the upregulation observed to NE was homologous. The increase in FABF during phentolamine was similar during guanadrel compared with placebo (guanadrel: 141 +/- 37 vs. placebo; 187 +/- 27% increase; P = 0.33), suggesting that there was at least partial compensation to maintain constant endogenous arterial

alpha-adrenergic tone. We conclude that there is homologous upregulation of arterial alpha-adrenergic responsiveness in humans when SNS activity is suppressed by guanadrel.

L19 ANSWER 4 OF 20 MEDLINE
ACCESSION NUMBER: 91206552 MEDLINE
DOCUMENT NUMBER: 91206552 PubMed ID: 1850202
TITLE: Regulation of venous alpha-adrenergic responses in older humans.
AUTHOR: Supiano M A; Hogikyan R V; Stoltz A M; Orstan N; Halter J B
CORPORATE SOURCE: Department of Internal Medicine, University of Michigan, Ann Arbor.
CONTRACT NUMBER: AG-00433 (NIA)
AG-08808 (NIA)
RR-00042 (NCRR)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1991 Apr) 260 (4 Pt 1) E599-607.
Journal code: 3U8; 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199105
ENTRY DATE: Entered STN: 19910607
Last Updated on STN: 19910607
Entered Medline: 19910517

AB Decreased adrenergic responsiveness in human aging could be a result of downregulation mediated by the age-related increase in sympathetic nervous system (SNS) tone. If so, suppression of SNS tone in elderly subjects should upregulate adrenergic responsiveness into the range observed for younger subjects. To test this hypothesis, we examined alpha 1 (phenylephrine)- and alpha 2 (clonidine)-adrenergic agonist-mediated venoconstriction in a group of 15 older healthy subjects (age 59-73 yr) during placebo and when SNS tone was suppressed by guanadrel (15 mg twice daily for 3 wk). During guanadrel compared with placebo 1) there were decreases in plasma norepinephrine (NE) levels (1.47 +/- 0.07 to 0.80 +/- 0.06 nM; P less than 0.001) and in the extravascular NE release rate derived from [3H]NE kinetics (11.8 +/- 1.4 to 6.1 +/- 1.0 nmol.min-1.m-2; P = 0.01), suggesting suppression of SNS tone; 2) there was an augmented clonidine-mediated venoconstriction response [analysis of variance (ANOVA) P = 0.01]; and 3) there was no detectable change in phenylephrine-mediated venoconstriction (ANOVA P = 0.60). When compared with previous results from young subjects, maximal alpha 2-adrenergic venoconstriction during guanadrel was decreased in the elderly compared with the young, although their response appeared to be appropriately upregulated by the decrease in SNS tone. The lack of an age-related decrease in alpha 1-adrenergic venoconstriction, together with the lack of upregulation of this response during guanadrel, suggests that regulation of this alpha 1-adrenergic response is impaired in the older group.

L19 ANSWER 5 OF 20 MEDLINE
ACCESSION NUMBER: 91157797 MEDLINE
DOCUMENT NUMBER: 91157797 PubMed ID: 2000792
TITLE: Comparison of the effects of guanadrel sulfate and propranolol on blood pressure, functional capacity, serum lipoproteins and glucose in systemic hypertension.
AUTHOR: Darga L L; Hakim M J; Lucas C P; Franklin B A
CORPORATE SOURCE: Division of Preventive and Nutritional Medicine, William Beaumont Hospital, Royal Oak, Michigan 48009.
SOURCE: AMERICAN JOURNAL OF CARDIOLOGY, (1991 Mar 15) 67 (7) 590-6.
Journal code: 3DQ; 0207277. ISSN: 0002-9149.
PUB. COUNTRY: United States
(CLINICAL TRIAL)

[redacted]

Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199104
ENTRY DATE: Entered STN: 19910428
Last Updated on STN: 19910428
Entered Medline: 19910410

AB In a controlled, double-blind, crossover study, the effects of guanadrel sulfate and propranolol on blood pressure (BP) and selected cardiopulmonary and metabolic variables were compared in 15 physically active and moderately hypertensive subjects. Guanadrel sulfate reduced systolic and diastolic BP at rest by -16 and -15 mm Hg, and at maximal exercise by -33 and -13 mm Hg, respectively (p less than 0.005), without affecting submaximal oxygen consumption (VO2), maximal VO2, ventilatory threshold, forced vital capacity, forced expiratory volume in 1 second, or fatigue, as assessed by perceived exertion. In contrast, propranolol significantly decreased diastolic BP at rest (-16 mm Hg) and systolic BP at maximal exercise (-44 mm Hg); however, it significantly decreased submaximal VO2 (-3.9 ml.kg-1.min-1), maximal VO2 (-3.9 ml.kg-1.min-1), ventilatory threshold (-0.3 liters.min-1), minute ventilation at submaximal exercise (-7.3 liters.min-1), forced expiratory volume in 1 second (-0.27 liters), and concomitantly increased the rating of perceived exertion at maximal exercise (1.9 U). Guanadrel sulfate was also associated with significant decreases in mean fasting plasma glucose and total serum cholesterol, whereas propranolol resulted in an increase in serum triglycerides (p less than 0.05). In contrast to propranolol, guanadrel sulfate appears to decrease BP without evoking negative metabolic consequences or impairing exercise tolerance.

L19 ANSWER 6 OF 20 MEDLINE
ACCESSION NUMBER: 91030359 MEDLINE
DOCUMENT NUMBER: 91030359 PubMed ID: 2171846
TITLE: Sensitization of human alpha 1- and alpha 2-adrenergic venous responses by guanadrel sulfate.
AUTHOR: Sekkarie M A; Egan B M; Neubig R R; Supiano M A
CORPORATE SOURCE: Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor 48109-0356.
CONTRACT NUMBER: DK 022748 (NIDDK)
HL01353 (NHLBI)
SOURCE: CLINICAL PHARMACOLOGY AND THERAPEUTICS, (1990 Nov) 48 (5) 537-43.
Journal code: DHR; 0372741. ISSN: 0009-9236.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199012
ENTRY DATE: Entered STN: 19910208
Last Updated on STN: 19910208
Entered Medline: 19901224

AB The alpha 1- and alpha 2-adrenergic venoconstriction in dorsal hand veins of normal subjects was determined by infusion of phenylephrine or clonidine. Oral administration of prazosin reduced the constriction response to phenylephrine but not to clonidine. Subjects were treated for 3 weeks in a randomized crossover design with placebo or guanadrel sulfate. Guanadrel reduced sympathetic tone (i.e., plasma norepinephrine and norepinephrine release rate), whereas venous responses to phenylephrine and clonidine were both augmented during guanadrel treatment. The effect on phenylephrine responses was primarily attributable to a decrease in the median effective concentration with a

small increase in maximum response. Clonidine showed a markedly increased maximum response with a small increase in the median effective concentration. Platelet alpha 2-adrenergic receptors increased slightly but there was no change in the amount of platelet pertussis toxin substrate during guanadrel treatment. Thus reduction in sympathetic tone in normal young men results in increased venous responses to both alpha 1- and alpha 2-agonists.

L19 ANSWER 7 OF 20 MEDLINE
ACCESSION NUMBER: 89234656 MEDLINE
DOCUMENT NUMBER: 89234656 PubMed ID: 2715368
TITLE: Disposition of guanadrel in subjects with normal and impaired renal function.
AUTHOR: Halstenson C E; Opsahl J A; Abraham P A; Schwenk M H; Andreadis N A; Antal E J; Matzke G R
CORPORATE SOURCE: Division of Nephrology, Hennepin County Medical Center, Minneapolis, Minnesota 55415.
SOURCE: JOURNAL OF CLINICAL PHARMACOLOGY, (1989 Feb) 29 (2) 128-32. Journal code: HT9; 0366372. ISSN: 0091-2700.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198906
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19900306
Entered Medline: 19890615

AB The disposition of a single 25 mg oral dose of guanadrel was evaluated in 22 subjects with various degrees of renal function. The terminal elimination half-life was significantly prolonged in subjects with a creatinine clearance (ClCr) less than 30 mL/min/1.73 m2 (19.2 +/- 16.8 h) compared to 3.7 +/- 1.9 h in subjects with a ClCr greater than 80 mL/min/1.73 m2. Apparent total body clearance (Clp/F) was also progressively lower in the patients with decreased renal function and the decline was significantly correlated with ClCr (Clp/F = 0.0294 + 0.0236 Clcr, r = 0.74, P = 0.002). Renal clearance and apparent nonrenal clearance also declined as creatinine clearance decreased, and both were significantly correlated with the observed ClCr. Apparent volume of distribution averaged 11.5 +/- 8.9 L/kg and did not differ in patients with decreased renal function compared to those with normal renal function. Thus, the disposition of guanadrel is significantly altered in the presence of renal insufficiency and dosage adjustments may be necessary, especially in patients with ClCr less than 50 ml/min.

L19 ANSWER 8 OF 20 MEDLINE
ACCESSION NUMBER: 88251200 MEDLINE
DOCUMENT NUMBER: 88251200 PubMed ID: 3382297
TITLE: Efficacy and safety of guanadrel in elderly hypertensive patients.
AUTHOR: Owens S D; Dunn M I
CORPORATE SOURCE: Division of Cardiovascular Disease, University of Kansas Medical Center, Kansas City 66103.
SOURCE: ARCHIVES OF INTERNAL MEDICINE, (1988 Jul) 148 (7) 1515-8. Journal code: 7FS; 0372440. ISSN: 0003-9926.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198807
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19900308
Entered Medline: 19880726

AB Hypertension is common in the elderly and is associated with higher

morbidity and mortality, which may be decreased by effective blood pressure control. Many antihypertensive drugs, however, are not well tolerated by the aged. We treated 21 patients (ten men and 11 women) between ages 65 and 84 years (mean, 73.6 years) with guanadrel sulfate. All patients had received prior antihypertensive therapy, which either was ineffective or caused undesirable side effects. Average follow-up time was 17 months. Mean systolic pressure on enrollment was 188 +/- 17 mm Hg and mean diastolic pressure was 100 +/- 10 mm Hg. After treatment, the mean systolic pressure was 139 +/- 15 mm Hg and mean diastolic pressure was 82 +/- 8 mm Hg. Dosage varied from 5 to 30 mg/d with a mean of 16 mg/d. The only significant side effects were fatigue, dizziness, and dyspnea reported in four patients. Eleven patients took the medication as monotherapy and ten received diuretics or diuretics and beta-blockers as additional therapy. Our conclusion is that guanadrel is an effective, well-tolerated medication for treatment of hypertension in the elderly.

L19 ANSWER 9 OF 20 MEDLINE
ACCESSION NUMBER: 89214449 MEDLINE
DOCUMENT NUMBER: 89214449 PubMed ID: 3243808
TITLE: Gas chromatographic determination of guanadrel in plasma and urine.
AUTHOR: Kaiser D G; Vangiessen G J; Shah J A; Weber D J
CORPORATE SOURCE: Drug Metabolism Research, Upjohn Company, Kalamazoo 49001.
SOURCE: JOURNAL OF CHROMATOGRAPHY, (1988 Dec 29) 434 (1) 135-43.
Journal code: HQF; 0427043. ISSN: 0021-9673.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198906
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19900306
Entered Medline: 19890608

AB To evaluate the pharmacokinetics and drug availability from various dosage formulations, a method for the determination of guanadrel, (1,4-dioxaspiro[4,5]dec-2-ylmethyl)guanidine, in plasma and urine was required. A gas chromatographic procedure, based on formation of a hexafluoroacetylacetone derivative in a two-phase system of water and toluene, was developed. The limit of determination of the method is 5 ng/ml guanadrel in plasma and 15 ng/ml guanadrel in urine. Statistical analyses indicate average recoveries of 98.1 +/- 18.0 and 104.4 +/- 15.6% from plasma and urine, respectively. Mass spectrometric analyses, in conjunction with gas chromatography, confirmed the specificity of the method for intact drug. The procedure was applied successfully to drug absorption studies in humans.

L19 ANSWER 10 OF 20 MEDLINE
ACCESSION NUMBER: 85290009 MEDLINE
DOCUMENT NUMBER: 85290009 PubMed ID: 4031111
TITLE: A dose-titration trial of guanadrel as step-two therapy in essential hypertension.
AUTHOR: Oren A; Rotmensch H H; Vlasses P H; Riley L J Jr; Koplin J R; Latini V; Ferguson R K
SOURCE: JOURNAL OF CLINICAL PHARMACOLOGY, (1985 Jul-Aug) 25 (5) 343-6.
Journal code: HT9; 0366372. ISSN: 0091-2700.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198509
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19900320

Entered Medline: 19850927

AB The efficacy and safety of low-dose guanadrel sulfate were evaluated in 20 patients with essential hypertension based on seated diastolic blood pressures (SDBP) ranging from 95 to 115 mm Hg despite a trial dosage of hydrochlorothiazide 50 mg/d for up to five weeks. These patients had been resistant to, or intolerant of, one or more step-two antihypertensive drugs in the past (i.e., methyldopa, beta-adrenergic blocking agents, clonidine, or prazosin). The majority of patients demonstrated a satisfactory response (SDBP 95 mm Hg or reduction in SDBP of 10 mm Hg) to guanadrel. Nine patients responded at a low dosage, 10 to 20 mg/d and remained free from adverse effects throughout the study (up to 12 weeks of treatment). Of the remaining 11 patients titrated to higher dosages of guanadrel (30 to 60 mg/d), three had no discernible response while six developed adverse effects. The results of the study suggest that guanadrel has an acceptable benefit-to-risk ratio only when used in low dosages (10 to 30 mg/d) and may be successfully employed as step-two antihypertensive therapy in patients resistant to, or intolerant of, other step-two agents.

L19 ANSWER 11 OF 20 MEDLINE
ACCESSION NUMBER: 85201973 MEDLINE
DOCUMENT NUMBER: 85201973 PubMed ID: 3158422
TITLE: Comparison on antihypertensive and cardiac effects of guanadrel and propranolol.
AUTHOR: Jiao P H; Allen J W
SOURCE: CHUNG-KUO I HSUEH KO HSUEH YUAN HSUEH PAO ACTA ACADEMIAE MEDICINAE SINICAE, (1985 Feb) 7 (1) 67-8.
Journal code: CZS; 8006230. ISSN: 1000-503X.
PUB. COUNTRY: China
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Chinese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198507
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19850709

L19 ANSWER 12 OF 20 MEDLINE
ACCESSION NUMBER: 85303909 MEDLINE
DOCUMENT NUMBER: 85303909 PubMed ID: 2412430
TITLE: Effects of exercise on blood pressure, plasma catecholamines, potassium and the electrocardiogram after diuretic and neural-blocking therapy for moderate hypertension.
AUTHOR: DeQuattro V; deGrau A; Foti A; Kim S J; DeQuattro E; Allen J
SOURCE: AMERICAN JOURNAL OF CARDIOLOGY, (1985 Aug 30) 56 (6) 39D-45D.
Journal code: 3DQ; 0207277. ISSN: 0002-9149.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198510
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19851003

AB Blood pressure control in mild and moderate hypertension may reduce morbidity and mortality. On the other hand, antihypertensive drugs may cause adverse metabolic, electrolyte, neural and hemodynamic alterations that detract from their effectiveness. The effect of hydrochlorothiazide (HCTZ) on some of these factors was compared with that of HCTZ and a sympatholytic drug in 20 hypertensive patients with left ventricular hypertrophy and retinopathy. HCTZ controlled blood pressure at rest and

during maximum treadmill exercise (-12 mm Hg systolic and diastolic pressure (p less than 0.05), reduced left ventricular mass by 7% (p less than 0.05) and lessened aerobic impairment at maximum treadmill exercise by 45% (p less than 0.05). These effects were further improved after "neural blockade." A potential adverse effect of HCTZ--hypokalemia (-0.6 mEq/liter, p less than 0.01)--and the associated incidence of ectopy during effort (50%) were lessened after neutralizing neural tone. Combination therapy with low-dose diuretic and sympatholytic drugs was effective and well tolerated in patients with cardiac and vascular sequelae of moderately severe hypertension.

L19 ANSWER 13 OF 20 MEDLINE
ACCESSION NUMBER: 85284647 MEDLINE
DOCUMENT NUMBER: 85284647 PubMed ID: 3896742
TITLE: Guanadrel. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in hypertension.
AUTHOR: Finnerty F A Jr; Brogden R N
SOURCE: DRUGS, (1985 Jul) 30 (1) 22-31. Ref: 22
Journal code: EC2; 7600076. ISSN: 0012-6667.
PUB. COUNTRY: Australia
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198510
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19970203
Entered Medline: 19851004

AB Guanadrel sulphate is an orally active peripheral sympathetic inhibitor (adrenergic neuron-blocking drug). In comparative studies, guanadrel was comparable in efficacy with guanethidine or methyldopa in mild to moderately severe hypertension, although generally it caused fewer central nervous system side effects than methyldopa and less orthostatic dizziness and diarrhoea than guanethidine. However, its efficacy in patients whose blood pressure remains inadequately controlled by other drugs (except diuretics alone) has yet to be adequately demonstrated. Guanadrel has a rapid onset of action and a half-life of about 10 hours, thus dose titration can be achieved more rapidly than with guanethidine, and twice daily administration is appropriate. Generally, guanadrel has been well tolerated, withdrawal of treatment due to adverse effects seldom being necessary. Thus, guanadrel appears to be a suitable alternative to methyldopa for the treatment of mild to moderately severe hypertension not controlled adequately by diuretics alone.

L19 ANSWER 14 OF 20 MEDLINE
ACCESSION NUMBER: 83206808 MEDLINE
DOCUMENT NUMBER: 83206808 PubMed ID: 6850722
TITLE: Comparison of guanadrel and guanethidine efficacy and side effects.
AUTHOR: Malinow S H
SOURCE: CLINICAL THERAPEUTICS, (1983) 5 (3) 284-9.
Journal code: CPE; 7706726. ISSN: 0149-2918.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198307
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19980206
Entered Medline: 19830715

AB Eighteen patients with essential hypertension uncontrolled by hydrochlorothiazide alone were randomly assigned to receive additional therapy with either guanadrel sulfate or guanethidine sulfate. The frequencies of morning orthostatic faintness, other orthostatic faintness, and diarrhea were twice as high in eight patients treated with guanethidine as in ten patients treated with guanadrel in a six-month comparison. The two drugs reduced blood pressure about equally well. In light of the efficacy without severe side effects, guanadrel may be an agent for step II therapy of hypertension.

L19 ANSWER 15 OF 20 MEDLINE
ACCESSION NUMBER: 84013685 MEDLINE
DOCUMENT NUMBER: 84013685 PubMed ID: 6621504
TITLE: Guanadrel (Hylorel)--a new antihypertensive drug.
AUTHOR: Anonymous
SOURCE: MEDICAL LETTER ON DRUGS AND THERAPEUTICS, (1983 Oct 14) 25 (646) 95-6.
Journal code: M52; 2985240R. ISSN: 0025-732X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198311
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19831123

L19 ANSWER 16 OF 20 MEDLINE
ACCESSION NUMBER: 83169179 MEDLINE
DOCUMENT NUMBER: 83169179 PubMed ID: 6762533
TITLE: Guanadrel sulfate compared with methyldopa for mild and moderate hypertension.
AUTHOR: Nugent C A; Palmer J D; Ursprung J J
SOURCE: PHARMACOTHERAPY, (1982 Nov-Dec) 2 (6) 378-83.
Journal code: PAR; 8111305. ISSN: 0277-0008.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198305
ENTRY DATE: Entered STN: 19900318
Last Updated on STN: 19900318
Entered Medline: 19830527

AB In a two-year study of 547 hypertensive patients receiving diuretics, the addition of guanadrel sulfate or methyldopa reduced elevated blood pressure to a similar degree and provided good control in 70% of the patients. Guanadrel-treated patients experienced less frequent and less severe drowsiness than methyldopa-treated patients. The frequency of morning orthostatic faintness was low and similar in both treatment groups. Guanadrel produced no tissue toxicity. Guanadrel sulfate, a postganglionic sympathetic inhibitor, is nearly free of central nervous system side effects and is recommended over methyldopa for step 2 therapy when diuretics alone fail to control mild or moderate hypertension.

L19 ANSWER 17 OF 20 MEDLINE
ACCESSION NUMBER: 81145662 MEDLINE
DOCUMENT NUMBER: 81145662 PubMed ID: 7206175
TITLE: Guanadrel. A new antihypertensive drug.
AUTHOR: Dunn M I; Dunlap J L
SOURCE: JAMA, (1981 Apr 24) 245 (16) 1639-42.
Journal code: KFR; 7501160. ISSN: 0098-7484.
PUB. COUNTRY: United States

[redacted]

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198105
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19900316
Entered Medline: 19810526

AB Guanadrel sulfate, a new adrenergic neuron inhibitor similar to guanethidine sulfate, was tested on 199 outpatients by 11 investigators. The patients had mild, moderate, or severe hypertension as determined by diastolic blood pressures of 95 to 105, 106 to 114, and 115 to 120 mm Hg, respectively. Guanadrel was found to be an effective antihypertensive agent for all levels of hypertension. Since guanadrel has a short onset of action and a short offset of action, which prevents many of the side effects of guanathidine, the dosage could be adjusted rapidly and safely. At low doses side effects are infrequent. There was no organ toxicity and no CNS effect. Guanadrel should be an effective step II or step III drug for treatment of hypertension.

L19 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:331316 CAPLUS
DOCUMENT NUMBER: 134:320885
TITLE: Administration of 5-HT receptor agonists and antagonists to treat premature ejaculation
INVENTOR(S): Smith, William L.; Doherty, Paul C., Jr.; Place, Virgil A.
PATENT ASSIGNEE(S): Vivus, Inc., USA
SOURCE: U.S., 13 pp., Cont.-in-part of U.S. 6,037,360.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6228864	B1	20010508	US 1998-181071	19981027
US 6037360	A	20000314	US 1997-959061	19971028
EP 1027011	A1	20000816	EP 1998-955189	19981028
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 2001008896	A1	20010719	US 2001-793839	20010226

PRIORITY APPLN. INFO.:
US 1997-958571 A2 19971028
US 1997-959061 A2 19971028
US 1998-181071 A 19981027
WO 1998-US22929 W 19981028

AB A method is provided for delaying the onset of ejaculation in an individual. The method preferably involves administration of an antidepressant drug, a serotonin agonist or antagonist, an adrenergic agonist or antagonist, an adrenergic neuron blocker, or a deriv. or analog thereof, within the context of an effective dosing regimen. The preferred mode of administration is transurethral; however, the selected active agent may also be delivered via intracavernosal injection or using alternative routes. Pharmaceutical formulations and kits are also provided.

IT **40580-59-4**, Guanadrel
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(5-HT receptor agonists and antagonists to treat premature ejaculation)
REFERENCE COUNT: 41

REFERENCE(S): (2) Anon; WO 9409828 1994 CAPLUS
(3) Anon; EP 781561 A1 1995 CAPLUS
(4) Anon; WO 9513072 1995 CAPLUS
(5) Anon; WO 9533048 1995 CAPLUS
(6) Anon; WO 9628142 1996 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:204251 CAPLUS
DOCUMENT NUMBER: 126:203737
TITLE: Antihypertensive combination of bisoprolol with .alpha.1-receptor blockers
INVENTOR(S): Jonas, Rochus
PATENT ASSIGNEE(S): Merck Patent Gmbh, Germany
SOURCE: Ger. Offen., 4 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19531463	A1	19970227	DE 1995-19531463	19950826

AB Combinations of the .beta.1-adrenergic receptor blocker bisoprolol with an .alpha.1-adrenergic receptor blocker selected from bunazosin, doxazocin, guanadrel, indoramin, ketanserin, prazosin, terazosin, trimazosin, and urapidil are useful for treatment of hypertension, heart failure, coronary heart disease, angina pectoris, and asthma. The combinations show an improved pharmacol. profile and spectrum of action and fewer side effects than prior art compns. Thus, suppositories are prepd. from a mixt. contg. bisoprolol 10, .alpha.1-receptor blocker 10, soybean lecithin 100, and cocoa butter 1400 g.

IT **40580-59-4**, Guanadrel
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(antihypertensive combination of bisoprolol with .alpha.1-receptor blockers)

L19 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:572042 CAPLUS
DOCUMENT NUMBER: 103:172042
TITLE: Action of drugs and chemical agents on rat liver regeneration
AUTHOR(S): Gershbein, Leon L.; Pedroso, Aldo F.
CORPORATE SOURCE: Northwest Inst. Med. Res., Chicago, IL, 60634, USA
SOURCE: Drug Chem. Toxicol. (1977) (1985), 8(3), 125-43
CODEN: DCTODJ; ISSN: 0148-0545
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A large no. (> 270) of drugs, chems., and other agents were tested for their effects on the regeneration of liver in hepatectomized rats. Seven anticonvulsants, 4 antiinflammatory drugs, 4 sedatives-hypnotics, the antipyretic-analgesic aminopyrine [58-15-1], the antifungal griseofulvin [126-07-8], a uricosuric, a muscle relaxant, a hydrocholeretic, an antihypertensive, and a thyroid inhibitor were hepatotrophic. Most the remaining drugs were inactive in this screening, whereas a few suppressed liver regeneration.

IT **40580-59-4**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(liver regeneration response to)

[redacted]

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DICTIONARY FILE UPDATES:  14 OCT 2001  HIGHEST RN 362009-74-3

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Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf


L20  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2001 ACS
RN   32059-15-7  REGISTRY
CN   Guanidine, [(octahydro-2-azocinyl)methyl]- (8CI, 9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Azocine, guanidine deriv.
OTHER NAMES:
CN   .alpha.-Guanidinomethylheptamethylenimine
CN   Guanazodine
FS   3D CONCORD
MF   C9 H20 N4
CI   COM
LC   STN Files:   BEILSTEIN*, BIOSIS, CA, CAPLUS, DDFU, DRUGU, EMBASE, MEDLINE,
       MRCK*, PHAR, PROMT, RTECS*, TOXLINE, TOXLIT, USAN
         (*File contains numerically searchable property data)
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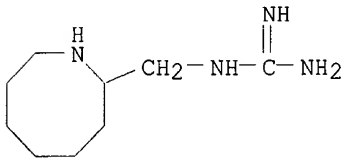


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

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             14 REFERENCES IN FILE CAPLUS (1967 TO DATE)


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L21           3 SEA FILE=MEDLINE ABB=ON  L20


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L22          14 SEA FILE=CAPLUS ABB=ON  L20
L23           2 SEA FILE=CAPLUS ABB=ON  L22(L)USES/RL


FILE 'MEDLINE' ENTERED AT 12:10:24 ON 15 OCT 2001

FILE 'CAPLUS' ENTERED AT 12:10:24 ON 15 OCT 2001
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PROCESSING COMPLETED FOR L21
PROCESSING COMPLETED FOR L23
L24           5 DUP REM L21 L23 (0 DUPLICATES REMOVED)
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                ANSWERS '4-5' FROM FILE CAPLUS

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L24  ANSWER 1 OF 5     MEDLINE
ACCESSION NUMBER:   81251273     MEDLINE
DOCUMENT NUMBER:    81251273   PubMed ID: 7257337
TITLE:              [Sanegyt therapy of moderately severe and severe arterial
                    hypertension].
                    Lechenie na sredno tezhka i tezhka arterialna khipertoniia
                    sus sanegit.
AUTHOR:             Stankusheva G; Elenkova A
SOURCE:             VUTRESHNI BOLESTI, (1981) 20 (2) 81-7.
                    Journal code: XMH; 0032666. ISSN: 0506-2772.
PUB. COUNTRY:       Bulgaria
                    Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           Bulgarian
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        198109
ENTRY DATE:         Entered STN: 19900316
                    Last Updated on STN: 19900316
                    Entered Medline: 19810915

L24  ANSWER 2 OF 5     MEDLINE
ACCESSION NUMBER:   81153838     MEDLINE
DOCUMENT NUMBER:    81153838   PubMed ID: 7209852
TITLE:              Blood-pressure depressing action of intravenous Sanegyt
                    (haemodynamic examinations).
AUTHOR:             Herpai Z; Simonyi J
SOURCE:             THERAPIA HUNGARICA, (1980) 28 (4) 181-5.
                    Journal code: VP3; 8706535. ISSN: 0133-3909.
PUB. COUNTRY:       Hungary
                    Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        198105
ENTRY DATE:         Entered STN: 19900316
                    Last Updated on STN: 19900316
                    Entered Medline: 19810526

L24  ANSWER 3 OF 5     MEDLINE
ACCESSION NUMBER:   81126928     MEDLINE
DOCUMENT NUMBER:    81126928   PubMed ID: 7466717
TITLE:              Study of the clinical effectivity of Sanegyt.
AUTHOR:             Dobi S; Siro B; Szabo T; Petranyi G
SOURCE:             THERAPIA HUNGARICA, (1980) 28 (2) 60-6.
                    Journal code: VP3; 8706535. ISSN: 0133-3909.
PUB. COUNTRY:       Hungary
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Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198104
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19900316
Entered Medline: 19810413

L24 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1978:16070 CAPLUS
DOCUMENT NUMBER: 88:16070
TITLE: Studies on the general pharmacological properties of guanazodine, [(octahydro-2-azocinyl)methyl]guanidine
AUTHOR(S): Iwata, Heitaroh; Yamamoto, Itaru; Kariya, Kimio; Shimizu, Takeshi; Hamakawa, Hiroshi; Kuroda, Kiyoshi; Tozuka, Tetsuo; Takayanagi, Noriyasu; Morishita, Daizaburo
CORPORATE SOURCE: Fac. Pharm. Sci., Osaka Univ., Suita, Japan
SOURCE: Oyo Yakuri (1977), 14(2), 235-49
CODEN: OYYAA2
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB The LD50 values of guanazodine (I) [32059-15-7] were 100 mg/kg (i.v.), 4300 mg/kg (orally) in male mice and 190 mg/kg (i.v.), >3670 mg/kg (orally) in male rats. Decreased spontaneous motor activity, ptosis, diarrhea, respiratory failure, and clonic convulsion were obsd. in mice and rats with a large dose of the drug. I showed no remarkable central actions except redn. of locomotor activity and prolongation of hexobarbital sleeping time in mice. It had no local anesthetic action and no effect on the neuromuscular junction of rats. The contraction of nictitating membrane of the cat elicited by elec. stimulation at the pre- and post-ganglionic fibers of the superior cervical sympathetic nerve was inhibited by I. This effect was antagonized by amphetamine. Small doses of I increased the propulsive motility of the small intestine in mice, however, the motility was inhibited by larger doses. In the dog, diarrhea was obsd. after I. In rabbits and cats, I produced a long lasting hypotension. Furthermore, a pressor effect and bradycardia elicited by the elec. stimulation of reticular formation of the cat were decreased by I. I had slightly pos. inotropic and chronotropic effects in isolated guinea pig heart. I showed no significant effect on the smooth muscle of the small intestine. I had an inhibitory effect on carragheenan-induced edema, however, this effect was not seen when the drug was administered for 2 days. I had a slight inhibition on rabbit platelet aggregation induced by collagen. Thus, I has pharmacol. actions similar, but in lesser potency, to those of guanethidine which was used as the ref. drug in this study.
IT **32059-15-7**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(pharmacol. of)

L24 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1977:561528 CAPLUS
DOCUMENT NUMBER: 87:161528
TITLE: Hypotensive effects of [(octahydro-2-azocinyl)methyl]guanidine (guanazodine)
AUTHOR(S): Shimizu, Takeshi; Hamakawa, Hiroshi; Tozuka, Tetsuo; Ohno, Hiroshi
CORPORATE SOURCE: Res. Lab., Toyo Jozo Co., Ltd., Shizuoka, Japan
SOURCE: Nippon Yakurigaku Zasshi (1976), 72(7), 837-50

Searched by Barb O'Bryen, STIC 308-4191

[redacted]

CODEN: NYKZAU
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB The hypotensive effect and the mechanism of action of guanazodine (I) [32059-15-7] were studied. I caused continuous hypotension in spontaneous hypertensive rats, in renal hypertensive dogs, and in renal hypertensive cats. The administration of I for 10 days did not decrease the hypotensive activity. I caused a slightly neg. chronotropic effect. The initial pressor effect of I was suppressed by .alpha.-adrenergic blockade with, phentolamine or phenoxybenzamine. I changed to hypotension the reflex hypertension caused by change to the orthostatic position in anesthetized cats. The pressor effect of noradrenaline [51-41-2] and tyramine in cats was enhanced by a low dose of I (3 mg/kg, i.v.), whereas it was suppressed by a high dose of I (10 mg/kg, i.v.). I relaxed the nictitating membrane in cats, inhibited the pos. chronotropic effect caused by pre- and post-synaptic stimulation of the cardiac sympathetic nerve in dogs, and inhibited the increase of the rhythmic movement of rabbit sinoauricular aorta caused by transmural elec. stimulation. The pos. inotropic effect in rabbit aorta caused by transmural elec. stimulation was suppressed by I, and this effect was inhibited by pretreatment with methamphetamine. I decreased the cardiac noradrenaline content in rat, but I did not affect the brain monoamine levels and adrenal monoamine level. The LD50 of I was 136 mg/kg, i.v. Thus, I appeared to cause hypotension through an adrenergic blocking action and a decrease of adrenergic tension caused by a decrease of the noradrenaline content in the sympathetic nerve. The potency and the duration of action of I were same as those of guanethidine and superior to those of bethanidine.

IT **32059-15-7**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(antihypertensive activity of, mechanism of)

```
=> fil reg
FILE 'REGISTRY' ENTERED AT 12:13:32 ON 15 OCT 2001
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DICTIONARY FILE UPDATES:  14 OCT 2001  HIGHEST RN 362009-74-3

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

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Crossover limits have been increased.  See HELP CROSSOVER see
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Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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E1            1     GUANIZIN/CN
E2            1     GUANLDINE, 1,1'-((OCTAHYDRO-2,6-NAPHTHALENEDIYLIDENE)DINITRI
                    LO)DI-, DIHYDROCHLORIDE/CN
E3            0 --> GUANOCHLOR/CN
E4            1     GUANOCHLORINE/CN
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=> s e5
L27           1 GUANOCLOR/CN

=> d ide

L27  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2001 ACS
RN   5001-32-1  REGISTRY
CN   Hydrazinecarboximidamide, 2-[2-(2,6-dichlorophenoxy)ethyl]- (9CI)  (CA
     INDEX NAME)
OTHER CA INDEX NAMES:
CN   Guanidine, [[2-(2,6-dichlorophenoxy)ethyl]amino]- (7CI, 8CI)
OTHER NAMES:
CN   Guanochlorine
CN   Guanoclor
FS   3D CONCORD
MF   C9 H12 Cl2 N4 O
CI   COM
LC   STN Files:   BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CHEMLIST,
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         (*File contains numerically searchable property data)
     Other Sources:   EINECS**, WHO
         (**Enter CHEMLIST File for up-to-date regulatory information)
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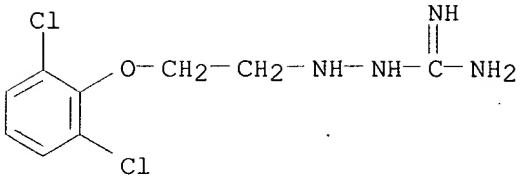

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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L29            3 SEA FILE=MEDLINE ABB=ON  L27



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FILE 'MEDLINE' ENTERED AT 12:15:33 ON 15 OCT 2001

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PROCESSING COMPLETED FOR L30
L31            4 DUP REM L29 L30 (0 DUPLICATES REMOVED)
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                 ANSWER '4' FROM FILE CAPLUS

=> d ibib ab 1-3; d ibib ab hitrn 4

L31  ANSWER 1 OF 4     MEDLINE
ACCESSION NUMBER:    94079939     MEDLINE
DOCUMENT NUMBER:     94079939   PubMed ID: 8257728
TITLE:               Spectrophotometric analysis of some guanidino drugs by
                     acid-dye and charge-transfer complexation methods.
AUTHOR:              Wahbi A A; Bedair M M; Galal S M; Gazy A A
CORPORATE SOURCE:    Faculty of Pharmacy, Pharmaceutical Analytical Chemistry
                     Department, University of Alexandria, Egypt.
SOURCE:              JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS, (1993
                     Aug) 11 (8) 639-45.
                     Journal code: A2C; 8309336. ISSN: 0731-7085.
PUB. COUNTRY:        ENGLAND: United Kingdom
                     Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         199401
ENTRY DATE:          Entered STN: 19940203
                     Last Updated on STN: 19940203
                     Entered Medline: 19940119
```

AB Two spectrophotometric methods are described for the determination of guanethidine sulphate (I), guanfacine hydrochloride (II), guanoclor sulphate (III), guanoxan sulphate (IV) and debrisoquine sulphate (V). The first method involves ion-pair formation of the selected compounds (I-V) with bromocresol purple at pH 3.8. The yellow ion pair is extracted with chloroform and the absorbance is measured at about 415 nm. The second method is based on the reaction of the basic guanidino compounds (I, III-V) with iodine in chloroform to give molecular charge-transfer complexes with maximum absorbance at 292 and 345 nm. Beer's law was obeyed for both methods and the relative standard deviations were found to be less than 2%. The apparent molar absorptivities were found to be 2.1 x 10(4) to 6.9 x 10(4) l mol-1 cm-1 using bromocresol purple and 0.7 x 10(4) to 2.4 x 10(4) l mol-1 cm-1 using iodine. The investigated drugs were assayed in tablets. The mean percentage recoveries were found to be 99.8-100.8% by the acid-dye method and around 100.4% by the charge-transfer complexation method.

L31 ANSWER 2 OF 4 MEDLINE
ACCESSION NUMBER: 89338580 MEDLINE
DOCUMENT NUMBER: 89338580 PubMed ID: 2527160
TITLE: Guanabenz, guanochlor, guanoxan and idazoxan bind with high affinity to non-adrenergic sites in pig kidney membranes.
AUTHOR: Vigne P; Lazdunski M; Frelin C
CORPORATE SOURCE: Centre de Biochimie du CNRS, Nice, France.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1989 Jan 31) 160 (2) 295-8.
Journal code: EN6; 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198909
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19970203
Entered Medline: 19890915

AB [3H]Idazoxan is a labelled ligand that is frequently used to study alpha 2-adrenoceptors in the central nervous system. In pig kidney membranes, [3H]idazoxan labelled high-affinity binding sites (Kd = 1.5 nM) that were not alpha 2-adrenoceptors and which recognized clonidine with low affinity. This new class of binding sites was recognized by amiloride derivatives; however, it is not likely that these sites are the well-known targets of amiloride in the kidney: the Na+/H+ exchanger and the epithelium Na+ channel. These binding sites may be the normal target of a series of imidazolidines derivatives (guanabenz, guanochlor, guanoxan), which are known for their antihypertensive properties.

L31 ANSWER 3 OF 4 MEDLINE
ACCESSION NUMBER: 86108328 MEDLINE
DOCUMENT NUMBER: 86108328 PubMed ID: 3002793
TITLE: Interaction of guanidinium and guanidinium derivatives with the Na+/H+ exchange system.
AUTHOR: Frelin C; Vigne P; Barbry P; Lazdunski M
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (1986 Jan 15) 154 (2) 241-5.
Journal code: EMZ; 0107600. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198603
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19980206
Entered Medline: 19860312

Searched by Barb O'Bryen, STIC 308-4191

AB Guanidinium, a small organic monovalent cation that is permeant through voltage-dependent cationic channels cannot be transported by the cardiac Na+/H+ exchange system. Yet it recognizes the exchanger and is able to block its activity (K0.5 = 30 mM). Guanidinium derivatives that do not belong to the amiloride series and which possess potent antihypertensive properties also block the activity of the Na+/H+ exchange system in various cell types with a greater potency than unsubstituted guanidinium. The most potent compound found, guanochlor, has an affinity for the exchanger ranging between 0.5 microM and 6 microM in different systems and is more potent than amiloride in all systems studied. Guanochlor has the same action as amiloride derivatives on the cardiac cells; it prevents intracellular pH recovery in cardiac cells that have been acidified and also antagonizes the effect of ouabain on 45Ca2+ uptake by chick cardiac cells. Guanochlor does not compete with [3H]ethylpropylamiloride for its binding to the Na+/H+ exchange system of rabbit kidney brush border membrane. It is suggested that guanochlor recognizes a binding site on the Na+/H+ exchanger that is distinct from the amiloride binding site.

L31 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1970:454285 CAPLUS
DOCUMENT NUMBER: 73:54285
TITLE: Antihypertensive activity of adrenergic neuron blocking agents
AUTHOR(S): Pelayo Cortines, Francisco; Tamargo Menendez, Juan
SOURCE: An. Real Acad. Farm. (1969), 35(4), 485-92
CODEN: ARAFAY
DOCUMENT TYPE: Journal
LANGUAGE: Spanish

AB Adrenergic neuron-blocking agents lower the arterial blood pressure and cause marked hypotension. This effect is due to impairment of conduction of impulses in adrenergic neurons with consequent failure of adrenaline and noradrenaline release. These compds. depress the end-organ responses to stimulation of all the postganglionic adrenergic nerves of the sympathetic nervous system but they do not depress the function of the postganglionic cholinergic nerves of this system. Expts. were based on the hypertensive effects produced by physostigmine on urethane-anesthetized rats. The compds. studied antagonized the pressor patterns induced by physostigmine. A brief account is presented of the technique used and the results obtained with guanoxan, guanachlor, and bethanidine. In some expts. the effects were recorded of the above-mentioned drugs on respiration, cardiac frequency, and electrocardiogram.

IT **5001-32-1**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(antihypertensive activity of)

=> fil reg; d ide
FILE 'REGISTRY' ENTERED AT 12:16:23 ON 15 OCT 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

STRUCTURE FILE UPDATES: 14 OCT 2001 HIGHEST RN 362009-74-3
DICTIONARY FILE UPDATES: 14 OCT 2001 HIGHEST RN 362009-74-3

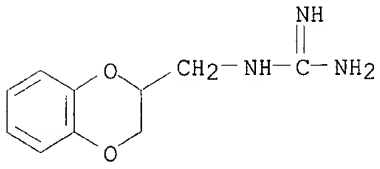
TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER see
HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES
for more information. See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

L32 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 2165-19-7 REGISTRY
CN Guanidine, [(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,4-Benzodioxin, guanidine deriv.
CN Guanidine, (1,4-benzodioxan-2-ylmethyl)- (7CI, 8CI)
OTHER NAMES:
CN (1,4-Benzodioxan-2-ylmethyl)guanidine
CN 2-(Guanidinomethyl)-1,4-benzodioxan
CN **Guanoxan**
CN Guanoxane
CN N-[(2,3-Dihydro-1,4-benzodioxin-2-yl)methyl]guanidine
FS 3D CONCORD
DR 46416-31-3
MF C10 H13 N3 O2
CI COM
LC STN Files: ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CHEMCATS, DDFU, DRUGU, EMBASE, IPA, MEDLINE, MRCK*, RTECS*, SPECINFO, TOXLINE, TOXLIT, USAN
(*File contains numerically searchable property data)
Other Sources: WHO



514/452

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

63 REFERENCES IN FILE CA (1967 TO DATE)
63 REFERENCES IN FILE CAPLUS (1967 TO DATE)
8 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> d que l33; d que l34; dup rem l33,l34
L32 1 SEA FILE=REGISTRY ABB=ON GUANOXAN/CN
L33 2 SEA FILE=CAPLUS ABB=ON L32(L)USES/RL

L32 1 SEA FILE=REGISTRY ABB=ON GUANOXAN/CN
L34 1 SEA FILE=MEDLINE ABB=ON L32

FILE 'CAPLUS' ENTERED AT 12:17:06 ON 15 OCT 2001

Searched by Barb O'Bryen, STIC 308-4191

[redacted]

FILE 'MEDLINE' ENTERED AT 12:17:06 ON 15 OCT 2001
PROCESSING COMPLETED FOR L33
PROCESSING COMPLETED FOR L34
L35 3 DUP REM L33 L34 (0 DUPLICATES REMOVED)
ANSWERS '1-2' FROM FILE CAPLUS
ANSWER '3' FROM FILE MEDLINE

=> d ibib ab hitrn 1-2; d ibib ab 3

L35 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:725447 CAPLUS
DOCUMENT NUMBER: 133:301178
TITLE: Use of CYP2D6 inhibitors in combination therapies
INVENTOR(S): Obach, Ronald Scott
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000059486	A2	20001012	WO 2000-IB304	20000320

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-128136 P 19990407
AB This invention relates to the use of a CYP2D6 inhibitor in combination with a drug having CYP2D6-catalyzed metab., wherein the drug and the CYP2D6 inhibitor are not the same compd.; and pharmaceutical compns. for said use.
IT **2165-19-7**, Guanoxan
RL: BAC (Biological activity or effector, except adverse); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); **USES (Uses)**
(use of CYP2D6 inhibitors in combination therapies)

L35 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1970:454285 CAPLUS
DOCUMENT NUMBER: 73:54285
TITLE: Antihypertensive activity of adrenergic neuron blocking agents
AUTHOR(S): Pelayo Cortines, Francisco; Tamargo Menendez, Juan
SOURCE: An. Real Acad. Farm. (1969), 35(4), 485-92
CODEN: ARAFAY
DOCUMENT TYPE: Journal
LANGUAGE: Spanish
AB Adrenergic neuron-blocking agents lower the arterial blood pressure and cause marked hypotension. This effect is due to impairment of conduction of impulses in adrenergic neurons with consequent failure of adrenaline and noradrenaline release. These compds. depress the end-organ responses

to stimulation of all the postganglionic adrenergic nerves of the sympathetic nervous system but they do not depress the function of the postganglionic cholinergic nerves of this system. Expts. were based on the hypertensive effects produced by physostigmine on urethane-anesthetized rats. The compds. studied antagonized the pressor patterns induced by physostigmine. A brief account is presented of the technique used and the results obtained with guanoxan, guanachlor, and bethanidine. In some expts. the effects were recorded of the above-mentioned drugs on respiration, cardiac frequency, and electrocardiogram.

IT **2165-19-7**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(antihypertensive activity of)

L35 ANSWER 3 OF 3 MEDLINE
ACCESSION NUMBER: 94079939 MEDLINE
DOCUMENT NUMBER: 94079939 PubMed ID: 8257728
TITLE: Spectrophotometric analysis of some guanidino drugs by acid-dye and charge-transfer complexation methods.
AUTHOR: Wahbi A A; Bedair M M; Galal S M; Gazy A A
CORPORATE SOURCE: Faculty of Pharmacy, Pharmaceutical Analytical Chemistry Department, University of Alexandria, Egypt.
SOURCE: JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS, (1993 Aug) 11 (8) 639-45.
Journal code: A2C; 8309336. ISSN: 0731-7085.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199401
ENTRY DATE: Entered STN: 19940203
Last Updated on STN: 19940203
Entered Medline: 19940119

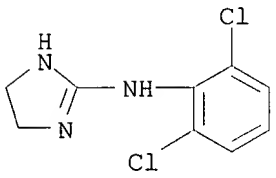
AB Two spectrophotometric methods are described for the determination of guanethidine sulphate (I), guanfacine hydrochloride (II), guanoclor sulphate (III), guanoxan sulphate (IV) and debrisoquine sulphate (V). The first method involves ion-pair formation of the selected compounds (I-V) with bromocresol purple at pH 3.8. The yellow ion pair is extracted with chloroform and the absorbance is measured at about 415 nm. The second method is based on the reaction of the basic guanidino compounds (I, III-V) with iodine in chloroform to give molecular charge-transfer complexes with maximum absorbance at 292 and 345 nm. Beer's law was obeyed for both methods and the relative standard deviations were found to be less than 2%. The apparent molar absorptivities were found to be 2.1 x 10(4) to 6.9 x 10(4) l mol-1 cm-1 using bromocresol purple and 0.7 x 10(4) to 2.4 x 10(4) l mol-1 cm-1 using iodine. The investigated drugs were assayed in tablets. The mean percentage recoveries were found to be 99.8-100.8% by the acid-dye method and around 100.4% by the charge-transfer complexation method.

=> d ide

L37 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN **4205-90-7** REGISTRY
CN 1H-Imidazol-2-amine, N-(2,6-dichlorophenyl)-4,5-dihydro- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2-Imidazoline, 2-(2,6-dichloroanilino)- (7CI, 8CI)
OTHER NAMES:

[redacted]

CN 2-(2,6-Dichloroanilino)-2-imidazoline
CN 2-(2,6-Dichlorophenylimino)imidazolidine
CN 734571A
CN Clonidin
CN Clonidine
CN M 5041T
CN SKF 34427
FS 3D CONCORD
DR 57066-25-8, 138474-59-6
MF C9 H9 Cl2 N3
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, NAPRALERT, NIOSHTIC, PHAR, PHARMASEARCH, PROMT, RTECS*, SPECINFO, TOXLINE, TOXLIT, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5769 REFERENCES IN FILE CA (1967 TO DATE)
52 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
5775 REFERENCES IN FILE CAPLUS (1967 TO DATE)
3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> d que l51
L44 10194 SEA FILE=MEDLINE ABB=ON CLONIDINE/CT
L46 823915 SEA FILE=MEDLINE ABB=ON REVIEW/DT
L49 2289 SEA FILE=MEDLINE ABB=ON L44(L)TU/CT
L50 1153 SEA FILE=MEDLINE ABB=ON L49/MAJ
L51 59 SEA FILE=MEDLINE ABB=ON L46 AND L50

=> sort l51 py a
SORT ENTIRE ANSWER SET? (Y)/N:y
PROCESSING COMPLETED FOR L51
L52 59 SORT L51 PY A

=> d ibib ab 1-15 -oldest 15 references

L52 ANSWER 1 OF 59 MEDLINE
ACCESSION NUMBER: 74093797 MEDLINE
DOCUMENT NUMBER: 74093797 PubMed ID: 4590881
TITLE: [Clonidine (Catapresan) in prevention of migraine].
Klonidin (Catapresan) profylaktisk mot migrene.
AUTHOR: Stensrud P; Sjaastad O
SOURCE: TIDSSKRIFT FOR DEN NORSKE LAEGEFORENING, (1973 Nov 30) 93

(33) 2423-5. Ref: 15
Journal code: VRV; 0413423. ISSN: 0029-2001.
PUB. COUNTRY: Norway
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: Norwegian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197404
ENTRY DATE: Entered STN: 19900310
Last Updated on STN: 19900310
Entered Medline: 19740403

L52 ANSWER 2 OF 59 MEDLINE
ACCESSION NUMBER: 76051182 MEDLINE
DOCUMENT NUMBER: 76051182 PubMed ID: 1102978
TITLE: Drug therapy: clonidine, a new antihypertensive drug.
AUTHOR: Pettinger W A
SOURCE: NEW ENGLAND JOURNAL OF MEDICINE, (1975 Dec 4) 293 (23) 1179-80. Ref: 22
Journal code: NOW; 0255562. ISSN: 0028-4793.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 197601
ENTRY DATE: Entered STN: 19900313
Last Updated on STN: 19900313
Entered Medline: 19760114

L52 ANSWER 3 OF 59 MEDLINE
ACCESSION NUMBER: 79091786 MEDLINE
DOCUMENT NUMBER: 79091786 PubMed ID: 366208
TITLE: Clonidine and central sympathetic nervous system blockaders.
AUTHOR: Ogino K
SOURCE: NIPPON RINSHO. JAPANESE JOURNAL OF CLINICAL MEDICINE, (1978 Nov 10) 36 (11) 3598-606. Ref: 24
Journal code: KIM; 0420546. ISSN: 0047-1852.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197903
ENTRY DATE: Entered STN: 19900315
Last Updated on STN: 19900315
Entered Medline: 19790324

L52 ANSWER 4 OF 59 MEDLINE
ACCESSION NUMBER: 78212830 MEDLINE
DOCUMENT NUMBER: 78212830 PubMed ID: 352519
TITLE: Recent acquisitions in antihypertensive therapy: clonidine, minoxidil and prazosin.
AUTHOR: Onesti G; Fernandes M
SOURCE: CARDIOVASCULAR CLINICS, (1978) 9 (1) 273-89. Ref: 71
Journal code: COL; 0213744. ISSN: 0069-0384.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197809

ENTRY DATE: Entered STN: 19900314
Last Updated on STN: 19900314
Entered Medline: 19780925

L52 ANSWER 5 OF 59 MEDLINE
ACCESSION NUMBER: 80036408 MEDLINE
DOCUMENT NUMBER: 80036408 PubMed ID: 386507
TITLE: The therapeutic uses of clonidine.
AUTHOR: Wood R A
SOURCE: SCOTTISH MEDICAL JOURNAL, (1979 Jul) 24 (3) 226-32. Ref: 39
Journal code: UJK; 2983335R. ISSN: 0036-9330.
PUB. COUNTRY: SCOTLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197912
ENTRY DATE: Entered STN: 19900315
Last Updated on STN: 19900315
Entered Medline: 19791229

L52 ANSWER 6 OF 59 MEDLINE
ACCESSION NUMBER: 81104133 MEDLINE
DOCUMENT NUMBER: 81104133 PubMed ID: 7006181
TITLE: The role of clonidine in the treatment of migraine: a review of the literature and personal experience.
AUTHOR: Hakkarainen H; Kokkanen E; Kallanranta T
SOURCE: UPSALA JOURNAL OF MEDICAL SCIENCES. SUPPLEMENT, (1980) 31 16-9. Ref: 19
Journal code: WRH; 0331622. ISSN: 0300-9726.
PUB. COUNTRY: Sweden
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198103
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19900316
Entered Medline: 19810324

L52 ANSWER 7 OF 59 MEDLINE
ACCESSION NUMBER: 81042885 MEDLINE
DOCUMENT NUMBER: 81042885 PubMed ID: 6107196
TITLE: [Therapy of essential arterial hypertension. V]. Terapia dell'ipertensione arteriosa essenziale. Parte v.
AUTHOR: Fossati C
SOURCE: CLINICA TERAPEUTICA, (1980 Jun 15) 93 (5) 577-94. Ref: 158
Journal code: DKN; 0372604. ISSN: 0009-9074.
PUB. COUNTRY: Italy
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: Italian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198101
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19950206
Entered Medline: 19810129

L52 ANSWER 8 OF 59 MEDLINE
ACCESSION NUMBER: 80186175 MEDLINE
DOCUMENT NUMBER: 80186175 PubMed ID: 6154838

TITLE: Clonidine in the treatment of hypertension.
AUTHOR: Garrett B N; Kaplan N M
SOURCE: JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, (1980) 2 Suppl 1 S61-71. Ref: 39
Journal code: K78; 7902492. ISSN: 0160-2446.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198007
ENTRY DATE: Entered STN: 19900315
Last Updated on STN: 19900315
Entered Medline: 19800728

AB Clonidine has clearly been shown to be effective in the treatment of all grades of hypertension. Clonidine by itself, when compared with placebo, has proved its worth in the treatment of essential hypertension; it has also been found to be more effective than diuretic treatment alone. When clonidine and a diuretic have been combined, the combination has proved superior to either clonidine or the diuretic given alone. The combination of clonidine with a diuretic is equal in efficacy to combinations of a diuretic with a beta-blocker, alpha-methyldopa, or prazosin. Combinations of a diuretic, a vasodilator, and clonidine were useful in patients with refractory hypertension that failed to respond to a two-drug regimen. Clonidine has also been shown to be effective in patients with renal failure or in hypertensive crisis.

L52 ANSWER 9 OF 59 MEDLINE
ACCESSION NUMBER: 80086206 MEDLINE
DOCUMENT NUMBER: 80086206 PubMed ID: 6101302
TITLE: Drugs five years later: clonidine.
AUTHOR: Lowenstein J
SOURCE: ANNALS OF INTERNAL MEDICINE, (1980 Jan) 92 (1) 74-7. Ref: 33
Journal code: 5A6; 0372351. ISSN: 0003-4819.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198002
ENTRY DATE: Entered STN: 19900315
Last Updated on STN: 19950206
Entered Medline: 19800226

AB Clonidine represents the prototype of a new class of centrally acting antihypertensive agents, classed as partial alpha-adrenergic antagonists. Blood pressure reduction is characterized, hemodynamically, by reduced cardiac output with unchanged peripheral vascular resistance at rest. Reflex control of blood pressure during orthostasis and exercise appears to be unimpaired, and orthostatic hypotension is uncommon. As with most other antihypertensive agents, satisfactory reduction of blood pressure with clonidine given as a sole agent is limited to patients with relatively mild hypertension; an additive or synergistic effect of diuretic administration has been well documented. Abrupt withdrawal of clinidine has been reported to be followed, within 24 to 36 h, by rebound hypertension, tachycardia, cardiac arrhythmias, and other changes suggestive of sympathetic overactivity. The incidence and clinical significance of rebound hypertension after abrupt cessation of clonidine therapy, and indeed the profile of blood pressure responses to varying physical activity during therapy, remain to be evaluated.

[redacted]

L52 ANSWER 10 OF 59 MEDLINE
ACCESSION NUMBER: 85043336 MEDLINE
DOCUMENT NUMBER: 85043336 PubMed ID: 6388273
TITLE: The sequential use of clonidine and naltrexone in the treatment of opiate addicts.
AUTHOR: Gold M S; Dackis C A; Washton A M
SOURCE: ADVANCES IN ALCOHOL AND SUBSTANCE ABUSE, (1984 Spring) 3 (3) 19-39. Ref: 121
Journal code: 2NZ; 8107172. ISSN: 0270-3106.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198411
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19980206
Entered Medline: 19841128

AB The efficacy of clonidine in the management of opiate withdrawal states has improved and refined the medical approach to this condition. In addition, the use of clonidine for opiate detoxification paves the way for naltrexone maintenance. Naltrexone, by providing chronic opiate receptor blockade, prevents opiate intoxication and subsequent readdiction in recovered addicts. The sequential use of clonidine and naltrexone, in conjunction with drug rehabilitation, appears to represent a viable and effective treatment for opiate addiction in motivated patients. The development of clonidine and naltrexone as treatment agents for opiate addiction also demonstrates that neurobiological advances can be translated into new and effective clinical approaches. This paper summarizes some of our experiences with the clonidine/naltrexone approach in motivated opiate addicts.

L52 ANSWER 11 OF 59 MEDLINE
ACCESSION NUMBER: 84137613 MEDLINE
DOCUMENT NUMBER: 84137613 PubMed ID: 6142084
TITLE: Psychiatric uses of antiadrenergic and adrenergic blocking drugs.
AUTHOR: Johnson J M
SOURCE: JOURNAL OF NERVOUS AND MENTAL DISEASE, (1984 Mar) 172 (3) 123-32. Ref: 111
Journal code: JAF; 0375402. ISSN: 0022-3018.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198404
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19980206
Entered Medline: 19840412

AB Most clinicians are aware of the unwanted behavioral effects which may accompany the use of drugs that affect noradrenergic functioning in the treatment of hypertension. However, it is not generally appreciated by psychiatrists that these drugs have many potential therapeutic uses in psychiatry and are potent adjuncts to traditional psychotropic drugs. When administered appropriately by a psychiatrist, antiadrenergic and adrenergic blocking drugs can be used for treatment of disorders of thought, mood, anxiety, and movement. This paper reviews the pharmacology of four of these medications. The literature is reviewed for each drug. Although the mechanisms of action of these antihypertensives differ, their common effects on noradrenergic functioning often result in behavioral changes.

L52 ANSWER 12 OF 59 MEDLINE
ACCESSION NUMBER: 86319379 MEDLINE
DOCUMENT NUMBER: 86319379 PubMed ID: 3529831
TITLE: Clonidine treatment of the opiate withdrawal syndrome. A review of clinical trials of a theory.
AUTHOR: Agren H
SOURCE: ACTA PSYCHIATRICA SCANDINAVICA. SUPPLEMENTUM, (1986) 327 91-113. Ref: 43
Journal code: 1W3; 0370365. ISSN: 0065-1591.
PUB. COUNTRY: Denmark
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198610
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19970203
Entered Medline: 19861015

L52 ANSWER 13 OF 59 MEDLINE
ACCESSION NUMBER: 86319374 MEDLINE
DOCUMENT NUMBER: 86319374 PubMed ID: 2875613
TITLE: Clonidine in abstinence reactions: basic mechanisms.
AUTHOR: Svensson T H
SOURCE: ACTA PSYCHIATRICA SCANDINAVICA. SUPPLEMENTUM, (1986) 327 19-42. Ref: 49
Journal code: 1W3; 0370365. ISSN: 0065-1591.
PUB. COUNTRY: Denmark
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198610
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19980206
Entered Medline: 19861015

L52 ANSWER 14 OF 59 MEDLINE
ACCESSION NUMBER: 86158009 MEDLINE
DOCUMENT NUMBER: 86158009 PubMed ID: 3513726
TITLE: Treatment of hypertensive emergencies and urgencies with oral clonidine loading and titration. A review.
AUTHOR: Houston M C
SOURCE: ARCHIVES OF INTERNAL MEDICINE, (1986 Mar) 146 (3) 586-9. Ref: 18
Journal code: 7FS; 0372440. ISSN: 0003-9926.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198603
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860328

AB Oral clonidine hydrochloride rapid titration or loading is a safe, effective method to control severe elevations of blood pressure in hypertensive crisis in many clinical situations. An initial oral dose of 0.1 to 0.2 mg of clonidine hydrochloride followed by hourly doses of 0.05 or 0.1 mg until goal blood pressure is attained that does not reduce perfusion to critical organs, or a total of 0.7 mg is given, will achieve

a significant reduction in blood pressure in 93% of patients. A smooth, rapid, predictable reduction in blood pressure, patient comfort, lower overall cost, reduced requirement for close observation, intravenous lines, and hospitalization, and a small incidence of clinically significant side effects make oral clonidine rapid titration an attractive oral antihypertensive agent for patients with hypertensive urgencies and in some carefully selected patients with hypertensive emergencies. Immediate outpatient follow-up within 24 hours is mandatory in all patients who are not hospitalized to adjust the dose of antihypertensive medications.

L52 ANSWER 15 OF 59 MEDLINE
ACCESSION NUMBER: 88160793 MEDLINE
DOCUMENT NUMBER: 88160793 PubMed ID: 3327372
TITLE: Clonidine and alcohol withdrawal.
AUTHOR: Cushman P Jr
CORPORATE SOURCE: Medical College of Virginia, Department of Psychiatry, McGuire VA Hospital, Richmond 23249.
SOURCE: ADVANCES IN ALCOHOL AND SUBSTANCE ABUSE, (1987) 7 (1) 17-28. Ref: 38
Journal code: 2NZ; 8107172. ISSN: 0270-3106.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198804
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19880421

AB Clonidine attenuates opiate withdrawal syndrome, via reduction in catecholamine activity in the brain, most probably at the locus ceruleus. Clonidine and locus ceruleus lesions, in animals with alcohol dependency as with the opiates, modify alcohol withdrawal. Both alcohol loading and withdrawal from steady alcohol use alter catecholamines in man and animals. Clonidine's potential to treat alcoholics in withdrawal is reviewed. Several double blind studies showed clonidine, or similar analogues, to be somewhat superior to placebo in acute alcohol withdrawal. Major improvements were in pulse, blood pressure and composite alcohol withdrawal scores. Side effects were minor and mainly included mild sedation, or postural hypotension. In the only available published study clonidine compared reasonably well to a standard sedative in alcohol withdrawal, and greatly influential in plasma catecholamine levels. Other components of alcohol withdrawal, as seizures and hallucinations-delirium tremens have not been documented to change with clonidine. The alpha-2-adrenergic agonists in alcohol treatment seemed modestly effective for treatment of some parts of alcohol withdrawal. They represent a promising, novel, but still investigational approach. Additional data, particularly comparing them to the benzodiazepines, are needed before their potential in therapeutics can be assessed.

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=> e atepamezole/cn
E1            1     ATENSINE/CN
E2            1     ATENUAL/CN
E3            0 --> ATEPAMEZOLE/CN
E4            1     ATEPARIN/CN
E5            1     ATEPAS K/CN
E6            1     ATEPAS OT 45/CN
E7            1     ATEPRINT E 9183/CN
E8            1     ATERIAN/CN
E9            1     ATERIOSAN/CN
E10           1     ATERM/CN
E11           1     ATERM M/CN
E12           1     ATEROCYN/CN

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L57  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2001 ACS
RN   104054-27-5  REGISTRY
CN   1H-Imidazole, 4-(2-ethyl-2,3-dihydro-1H-inden-2-yl)- (9CI)  (CA INDEX
     NAME)
OTHER NAMES:
CN   Atipamezole
CN   MPV 1248
FS   3D CONCORD
MF   C14 H16 N2
CI   COM
SR   CA
LC   STN Files:   ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS,
       BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CIN, DDFU,
       DRUGNL, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT,
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     Other Sources:   WHO
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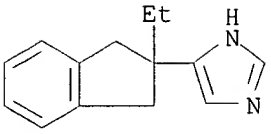

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

207 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
208 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> d que l61
L57 1 SEA FILE=REGISTRY ABB=ON ATIPAMEZOLE/CN
L58 252 SEA FILE=MEDLINE ABB=ON L57
L59 115 SEA FILE=MEDLINE ABB=ON ATIPAMEZOLE/TI
L60 113 SEA FILE=MEDLINE ABB=ON L58 AND L59
L61 1 SEA FILE=MEDLINE ABB=ON REVIEW/DT AND L60

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L61 ANSWER 1 OF 1 MEDLINE
ACCESSION NUMBER: 89390301 MEDLINE
DOCUMENT NUMBER: 89390301 PubMed ID: 2571275
TITLE: Pharmacological profiles of medetomidine and its antagonist, **atipamezole**.
AUTHOR: Virtanen R
SOURCE: ACTA VETERINARIA SCANDINAVICA. SUPPLEMENT, (1989) 85 29-37.
Ref: 30
Journal code: 27Y; 0061331. ISSN: 0065-1699.
PUB. COUNTRY: Norway
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198910
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 20000303
Entered Medline: 19891019

AB Medetomidine, (+/-)-4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole, is a very potent, selective and specific full agonist at both pre- and postsynaptic alpha 2-adrenoceptors as demonstrated in several models both in vitro and in vivo. In receptor binding experiments the alpha 2/alpha 1 selectivity ratio of medetomidine is 1620 compared to 260, 220 and 160 for detomidine, clonidine and xylazine, respectively. The alpha 2-adrenoceptor activity of medetomidine resides predominantly in its d-enantiomer (dexmedetomidine). Medetomidine induces a dose-dependent decrease in the release and turnover of noradrenaline, dopamine and serotonin in the CNS as measured by changes in metabolite concentrations or using pharmacological intervention techniques. Inhibition of sympathetic tone in the CNS by medetomidine leads for a characteristic pattern of pharmacodynamic responses including e.g. hypotension, bradycardia, sedation, relief of anxiety, analgesia and hypothermia. The potent, dose-dependent sedative effects of medetomidine have been demonstrated in several classical animal models (e.g. decrease in spontaneous motility in rats and mice, potentiation of barbiturate-induced anaesthesia in rats and mice, induction of sleep in young chicks). At high doses medetomidine has

hypnotic of anaesthetic effects, a property which distinguishes it clearly from detomidine, clonidine and other alpha 2-agonists. The pharmacological, neurochemical and behavioral effects of medetomidine can be inhibited by prior, simultaneous of subsequent administration of a selective and specific alpha 2-antagonist, atipamezole. Besides verifying that the main pharmacodynamic effects of medetomidine are alpha 2-mediated, this finding forms a strong basis for the use of atipamezole as a reversing agent against medetomidine-induced effects in veterinary practice.

=> d que l62
L57 1 SEA FILE=REGISTRY ABB=ON ATIPAMEZOLE/CN
L62 118 SEA FILE=CAPLUS ABB=ON L57(L)(THU OR BAC)/RL

=> sort l62 py a 1-
PROCESSING COMPLETED FOR L62
L64 118 SORT L62 1- PY A

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L64 ANSWER 1 OF 118 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1990:526464 CAPLUS
DOCUMENT NUMBER: 113:126464
TITLE: Pharmacological effects and pharmacokinetics of atipamezole, a novel .alpha.2-adrenoceptor antagonist - a randomized, double-blind cross-over study in healthy male volunteers
AUTHOR(S): Karhuvaara, Sakari; Kallio, Antero; Scheinin, Mika; Anttila, Markku; Salonen, Jarmo S.; Scheinin, Harry
CORPORATE SOURCE: Dep. Pharmacol., Univ. Turku, Turku, Finland
SOURCE: Br. J. Clin. Pharmacol. (1990), 30(1), 97-106
CODEN: BCPHBM; ISSN: 0306-5251
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Single doses (10, 30, and 100 mg) of atipamezole (MPV-1248, I), a new potent and selective imidazole-type .alpha.2-adrenoceptor antagonist, were administered as 20-min i.v. infusions to six healthy men. Later, 100 mg atipamezole was given orally to the same subjects. The i.v. doses created linearly dose-related concns. of atipamezole in blood plasma. Pharmacokinetic calcns. revealed an elimination half-life of 1.7-2.0 h, an apparent vol. of distribution of 3.0-3.5 L/kg, and a total plasma clearance of 1.1-1.5 L/h.kg. No atipamezole could be detected in plasma after oral dosing. Subjective drug effects were seen mainly after the largest i.v. dose and included increased alertness and nervousness, coldness and sweating of hands and feet, tremor and shivering, motor restlessness, and increased salivation. Salivation was also quantitated using dental cotton rolls, with dose-related increases produced by the i.v. doses. The 100 mg i.v. dose increased plasma noradrenaline concns. by 484%, and also elevated both systolic and diastolic blood pressure by 17 and 14 mm Hg, resp. The 30-mg dose had minor and the 10-mg dose no effects on these variables. Adrenaline and cAMP levels in plasma were increased only after the largest dose. No drug effects were obsd. after oral dosing. Plasma C-peptide and blood glucose levels were not markedly influenced and cortisol secretion was not stimulated by the drug. The effects are compatible with the presumed .alpha.2-adrenoceptor antagonistic action of atipamezole and are in general concordance with the effects of other .alpha.2-adrenoceptor antagonists (yohimbine and idazoxan). Although not orally active, atipamezole may be a useful agent in studies of .alpha.2-adrenoceptor function in man.
IT **104054-27-5**, Atipamezole
RL: **BAC (Biological activity or effector, except adverse)**; BIOL

(Biological study)
(pharmacokinetics and .alpha.2-adrenoceptor antagonist effects of, in humans)

L64 ANSWER 2 OF 118 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:526947 CAPLUS
DOCUMENT NUMBER: 115:126947
TITLE: Anorectic effect of alpha2-antagonists in dog: effect of acute and chronic treatment
AUTHOR(S): Berlan, Michel; Galitzky, Jean; Tran, Marie Antoinette; Montastruc, Paul
CORPORATE SOURCE: Lab. Pharmacol. Med., Fac. Med., Toulouse, 31073, Fr.
SOURCE: Pharmacol., Biochem. Behav. (1991), 39(2), 313-20
CODEN: PBBHAU; ISSN: 0091-3057
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Acute oral administration of .alpha.2-antagonists (yohimbine, RX 821002, atipamezole: 1 mg/kg each) reduced dog food intake. Yohimbine reduced food intake over 20 h, while the effect of the 2 other drugs lasted only 2 h. Yohimbine (0.4 or 1 .mu.g/kg) gave the same results. At these doses, it promoted a lasting durable increase in plasma nonesterified fatty acids and catecholamines levels and a transient elevation of plasma insulin levels. The .beta.-antagonist nadolol (4 mg/kg orally) suppressed the yohimbine-induced lipid mobilization without modifying its anorectic effect. Chronic oral yohimbine (0.4 mg/kg/day during 14 days) reduced food intake and promoted a wt. loss. Normal food intake was recovered 2 days after yohimbine withdrawal. No change was obsd. in the no. of platelet .alpha.2-adrenergic receptors. In addn. to their lipid mobilizing action and sympathetic tone stimulation, .alpha.2-antagonist compds. reduce food intake.
IT **104054-27-5**, Atipamezole
RL: **BAC (Biological activity or effector, except adverse)**; BIOL (Biological study)
(anorectic activity of, mechanism of)

L64 ANSWER 3 OF 118 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:286157 CAPLUS
DOCUMENT NUMBER: 122:71801
TITLE: Increased airway pressure in response to xylazine is inhibited by both atipamezole and atropine in sheep
AUTHOR(S): Papazoglou, L.; Raptopoulos, D.; Kokolis, N.
CORPORATE SOURCE: Veterinary School, Aristotle University Thessaloniki, Thessaloniki, GR-54627, Greece
SOURCE: J. Vet. Med., Ser. A (1994), 41(7), 568-72
CODEN: JVMAE6; ISSN: 0931-184X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect on airway pressure of xylazine alone or following the administration of atipamezole or atropine was studied in 31 halothane-anesthetized sheep. Xylazine produced a significant increase in airway pressure which lasted for at least 30 min. This effect was inhibited by both atipamezole and atropine. The results suggest that the xylazine-induced increase in airway pressure in sheep is .alpha.2-adrenergically mediated. Moreover, activation of central .alpha.2-adrenoceptors leading to vagal stimulation may be involved.
IT **104054-27-5**, Atipamezole
RL: **BAC (Biological activity or effector, except adverse)**; BIOL (Biological study)
(atipamezole and atropine inhibition of xylazine-induced airway pressure increase in relation to .alpha.2-adrenergic mediation)

L64 ANSWER 4 OF 118 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:265015 CAPLUS

DOCUMENT NUMBER: 122:46247
TITLE: Use of atipamezole to reverse xylazine tranquilization in captive Arabian oryx (Oryx leucoryx)
AUTHOR(S): Ancrenaz, Marc
CORPORATE SOURCE: National Wildlife Research Center, National Commission Wildlife Conservation and Development, Taif, Saudi Arabia
SOURCE: J. Wildl. Dis. (1994), 30(4), 592-5
CODEN: JWIDAW; ISSN: 0090-3558
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Twenty-seven hand-reared male Arabian oryx (Oryx leucoryx), with a mean (.+-.SD) wt. of 86.9 (.+-.16.9) kg, were darted in the muscle with xylazine at a mean (.+-.SD) dosage rate of 0.5 (.+-.0.07) mg/kg. This dosage was sufficient to induce recumbency in 24 animals in a mean (.+-.SD) time of 9.4 (.+-.5.6) min. Three animals never became recumbent at this dosage but were mildly sedated and still could be handled. Atipamezole was used as antagonist agent in a mean (.+-.SD) time of 32.1 (.+-.9.6) min after the initial injection of xylazine. Two thirds of the total amt. of atipamezole was given i.v. while one third was injected s.c. at a mean (.+-.SD) total dosage of 0.087 (.+-.0.014) mg/kg. The mean (.+-.SD) reversal time (time to stand up after the injection of atipamezole) was 87.1 (.+-.43.2) sec for the 24 recumbent oryx. A resedation period (lowering of the ears and the head, unsteady gait and sometimes recumbency), lasting up to two hours, occurred between two and five hours after the injection of atipamezole in 21 animals.

IT **104054-27-5**, Atipamezole
RL: **BAC (Biological activity or effector, except adverse)**; BIOL (Biological study)
(atipamezole for reversal of xylazine tranquilization in captive Arabian oryx)

L64 ANSWER 5 OF 118 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:252043 CAPLUS
DOCUMENT NUMBER: 122:23562
TITLE: Potentiation of the antiobesity effect of the selective .beta.3-adrenoceptor agonist BRL 35135 in obese Zucker rats by exercise
AUTHOR(S): Santti, Eriika; Huupponen, Risto; Rouru, Juha; Haenninen, Virve; Pesonen, Ullamari; Jhanwar-Uniyal, Meena; Koulu, Markku
CORPORATE SOURCE: Dept. Pharmacology, Univ. Turku, Turku, Finland
SOURCE: Br. J. Pharmacol. (1994), 113(4), 1231-6
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of chronic treatments with a selective .beta.3-adrenoceptor agonist and a selective .alpha.2-adrenoceptor antagonist and their interactions with phys. exercise training were studied in exptl. obesity. BRL 35135 (.beta.3-agonist, 0.5 mg/kg/day, orally), atipamezole (.alpha.2-antagonist, 4.0 mg/kg/day, orally) and placebo were given to genetically obese male Zucker rats. Half of the rats were kept sedentary whereas the other half were subjected to moderate treadmill exercise training. Boty wt. gain, cumulative food intake, the neuropeptide Y content of the hypothalamic paraventricular nucleus, brown adipose tissue thermogenic activity (measured as GDP binding), and plasma insulin and glucose levels were measured after 3-wk treatment and exercise. Treatment with BRL 35135 reduced wt. gain by 19%, increased brown adipose tissue thermogenic activity 45-fold and reduced plasma insulin by 50%. Atipamezole slightly increased food intake and neuropeptide Y content in the paraventricular hypothalamic nucleus but had no effect on the other parameters measured. Exercise alone had no effect on wt. gain, food intake or thermogenic activity, whereas it reduced plasma insulin and

glucose levels. The effect of BRL 35135 on wt. gain and thermogenic activity was potentiated by exercise: the redn. in wt. gain was 56% in comparison with 19% in sedentary animals. Food intake was reduced in the BRL 35135-treated-exercise-trained animals, although neither the .beta.3-agonist nor exercise alone affected it. Based on these results in genetically obese Zucker rats, combination of .beta.3-agonist treatment with a moderate phys. training may offer a new feasible approach to the therapy of obesity.

IT **104054-27-5**, Atipamezole
RL: **BAC (Biological activity or effector, except adverse)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(.beta.3-adrenergic agonist BRL 35135 plus .alpha.2-adrenergic antagonist atipamezole plus exercise treatment of obesity)

L64 ANSWER 6 OF 118 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:231962 CAPLUS
DOCUMENT NUMBER: 122:23654
TITLE: Some unusual effects of .alpha.2-adrenergic drugs on cortical high voltage spindles in rats
AUTHOR(S): Yavich, L.; Sirvioe, J.; Haapalinna, A.; Riekkinen Sr., P.
CORPORATE SOURCE: Department of Neurology, University of Kuopio, P.O. Box 1627, Kuopio, 70211, Finland
SOURCE: Eur. Neuropsychopharmacol. (1994), 4(4), 535-8
CODEN: EURNE8; ISSN: 0924-977X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The dose-response curves for a no. of .alpha.-adrenergic drugs were investigated to est. a possible role of the .alpha.2/.alpha.1 selectivity of these drugs on the incidence of cortical high voltage spindles (HVS), reflecting level of vigilance. The .alpha.2 antagonists yohimbine (0.25-4 mg/kg) and idazoxan (0.5-4 mg/kg), but not atipamezole induced a biphasic effect on the incidence of HVS in rats. This effect of relatively small doses of yohimbine and idazoxan should be taken into consideration when using these drugs as .alpha.2 antagonists in behavioral and neurophysiol. tests. On the other hand the linearity of the dose-response curve for atipamezole (0.01-4 mg/kg) indicates that this drug is a good candidate for use in such tests.

IT **104054-27-5**, Atipamezole
RL: **BAC (Biological activity or effector, except adverse)**; BIOL (Biological study)
(.alpha.2-adrenergic drugs effect on cerebral cortical high voltage spindles in absence epilepsy model)

L64 ANSWER 7 OF 118 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:223489 CAPLUS
DOCUMENT NUMBER: 122:23603
TITLE: Antagonistic effects of atipamezole on medetomidine-midazolam induced sedation in dogs
AUTHOR(S): Hayashi, Kei; Nishimura, Ryohei; Yamaki, Akira; Kim, Hwi-yool; Matsunaga, Satoru; Sasaki, Nobuo; Takeuchi, Akira
CORPORATE SOURCE: Faculty of Agriculture, University of Tokyo, Tokyo, 113, Japan
SOURCE: J. Vet. Med. Sci. (1994), 56(5), 1009-11
CODEN: JVMSEQ; ISSN: 0916-7250
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The antagonistic effect of atipamezole (80 .mu.g/kg) on medetomidine (20 .mu.g/kg)-midazolam (0.3 mg/kg) induced sedation was evaluated in dogs. Atipamezole effectively reversed sedation and significantly shortened arousal time and total recovery time without apparent side effects. Atipamezole also effectively reversed changes in heart rate, respiratory

rate and body temp. produced by medetomidine-midazolam. The possible use of atipamezole as a reversal agent might enhance the value of medetomidine-midazolam as a chem. restraint agent in dogs.

IT **104054-27-5**, Atipamezole
RL: **BAC (Biological activity or effector, except adverse)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antagonistic effects of atipamezole on medetomidine-midazolam induced sedation in dogs)

L64 ANSWER 8 OF 118 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:692510 CAPLUS
DOCUMENT NUMBER: 121:292510
TITLE: Antagonistic effects of atipamezole on medetomidine-induced sedation in cats
AUTHOR(S): Nakamura, Kazuo; Endo, Hiroshi; Mizuno, Masao; Minato, Etsuko; Yoshida, Toshinobu; Kazaki, Hiroyasu; Tomizawa, Nobuyuki; Hara, Shigeo
CORPORATE SOURCE: Fac. Agric., Iwate Univ., Morioka, 020, Japan
SOURCE: Iwate Daigaku Nogakubu Hokoku (1994), 21(4), 261-9
CODEN: IDNHAR; ISSN: 0579-2746
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB Atipamezole (ATP) was i.m. injected to cats pretreated i.m. with 100 and 150 .mu.g/kg of medetomidine (MDT) at 200 and 400 .mu.g/kg and 300 and 600 .mu.g/kg, resp., 40 min after MDT treatment. Deeply sedated cats raised their heads in a 1-4 min and showed total recovery in 5-10 min after ATP injection. Soon after ATP injection, increases in heart and respiratory rates and recovery of most reflexes were obsd. that lead to quick and smooth arousal. There was no difference in the reversal effect between 2 doses of ATP in each dose of MDT. On the other hand, excitement, changes in breathing, hyperesthesia, and urination were obsd. in cats treated with 600 .mu.g/k of ATP alone.

IT **104054-27-5**, Atipamezole
RL: **BAC (Biological activity or effector, except adverse)**; BIOL (Biological study)
(antagonistic effects of atipamezole on medetomidine-induced sedation in cats)

L64 ANSWER 9 OF 118 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:672054 CAPLUS
DOCUMENT NUMBER: 121:272054
TITLE: Atipamezole, an alpha2 antagonist, augments opiate-induced muscle rigidity in the rat
AUTHOR(S): Weinger, Matthew B.; Bednarczyk, Julie Miriam
CORPORATE SOURCE: Dep. Anesthesiol., Univ. California, San Diego, CA, USA
SOURCE: Pharmacol., Biochem. Behav. (1994), 49(3), 523-9
CODEN: PBBHAU; ISSN: 0091-3057
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Atipamezole is a new, highly selective alpha2-adrenoceptor antagonist currently undergoing clin. trials as an antagonist for dexmedetomidine, a potent alpha2 agonist with sedative and analgesic properties. It has previously been demonstrated that dexmedetomidine, acting at central alpha2 adrenoceptors, antagonizes opiate-induced muscle rigidity. However, the role of endogenous alpha2-adrenergic systems in opiate-induced rigidity remains to be elucidated. The present study was designed to assess the effects of atipamezole on basal muscle tone and on alfentanil-induced muscle rigidity in the rat. Muscle tone was measured using gastrocnemius electromyog. (EMG). After a 15-min baseline, saline or atipamezole (0.3 or 1.0 mg/kg) was administered, and 10 min later, saline or alfentanil (50, 150, or 300 .mu.g/kg) was injected s.c. Data were collected for an addnl. 60 min. Atipamezole (1.0 mg/kg) pretreatment

[redacted]

(in the absence of alfentanil) produced a small increase in tonic EMG activity when compared with saline pretreatment. After saline pretreatment, significant muscle rigidity occurred in the two highest alfentanil dose groups. Atipamezole (0.3 and 1.0 mg/kg) augmented alfentanil-induced muscle rigidity. The ability of the alpha2 antagonist to potentiate both basal muscle tone and alfentanil-induced rigidity suggests that endogenous adrenergic activity and/or direct alpha2-adrenoceptor interaction with opioid receptors mediate opiate-induced muscle rigidity. These findings may be of clin. as well as basic neuropharmacol. interest.

IT **104054-27-5**, Atipamezole
RL: **BAC (Biological activity or effector, except adverse)**; BIOL (Biological study)
(.alpha.2-adrenergic antagonist atipamezole augments opiate-induced muscle rigidity in rat)

L64 ANSWER 10 OF 118 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:275350 CAPLUS
DOCUMENT NUMBER: 124:332639
TITLE: Cardiovascular effects of medetomidine-ketamine anesthesia in sheep, with and without 100% oxygen, and its reversal with atipamezole.
AUTHOR(S): Tulamo, Riitta-Mari; Raekallio, Jarja; Ekblad, Anneli
CORPORATE SOURCE: Faculty Veterinary Medicine, Helsinki University, FIN-00014, Finland
SOURCE: J. Vet. Anaesth. (1995), 22, 9-14
CODEN: JVANEJ; ISSN: 1351-6574
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The cardiovascular effects of i.v. administered medetomidine 20 .mu.g/kg bodyweight (bwt) and ketamine (2 mg/kg bwt), with and without 100% inspired oxygen, were investigated in six domestic sheep. A second dose of medetomidine and ketamine was administered i.v., at dose 10 .mu.g/kg bwt and 1 mg/kg bwt resp., 25 min after the initial injection. Heart rate, PaO2, pH and Hb satn. decreased whereas PaCO2 and base excess increased post-injection. Transient hypertension and an increase in respiration rate were evident within the first 10 min of anesthesia. Significant hypoxemia ($P<0.01$) developed in sheep breathing room air. Inspired 100% oxygen improved PaO2 (but the difference was not significant), and improved Hb satn. significantly ($P<0.05$), however, this effect varied between individuals. One sheep breathing room air suffered a cardiac arrest immediately postinjection and had to be resuscitated. Atipamezole 125 .mu.g/kg given i.m. 45 min after the initial injection rapidly reversed the effects of medetomidine. Recovery times did not significantly differ although time to extubation and standing tended to be longer in sheep breathing room air compared to the sheep breathing 100% oxygen. The quality of the recovery did not differ.

IT **104054-27-5**, Atipamezole
RL: **BAC (Biological activity or effector, except adverse)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(cardiovascular effects of medetomidine-ketamine anesthesia in sheep, with and without 100% oxygen, and reversal with atipamezole)

L64 ANSWER 11 OF 118 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:22867 CAPLUS
DOCUMENT NUMBER: 124:135473
TITLE: Further characterization of the receptor mechanism involved in the antidysrhythmic effect of dexmedetomidine on halothane/epinephrine dysrhythmias in dogs
AUTHOR(S): Kamibayashi, Takahiko; Mammoto, Tadanori; Hayashi, Yukio; Yamatodani, Atsushi; Takada, Koji; Sasaki, Shigeta; Yoshiya, Ikuto

CORPORATE SOURCE: Faculty Medicine, Osaka University, Suita, 565, Japan
SOURCE: Anesthesiology (1995), 83(5), 1082-9
CODEN: ANESAV; ISSN: 0003-3022
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It was previously reported that dexmedetomidine, a selective .alpha.2-agonist, prevents the genesis of halothane-epinephrine dysrhythmias through a central mechanism. Because dexmedetomidine also binds to imidazoline receptors, the current study was performed to examine the precise receptor mechanism involved in the antidysrhythmic property of dexmedetomidine. Dogs were anesthetized with halothane (1.3%) and monitored continuously for systemic arterial pressure and premature ventricular contractions. The dysrhythmogenic dose of epinephrine was defined as the smallest dose producing .gtoreq.4 premature ventricular contractions within a 5-s period. The antidysrhythmic action of dexmedetomidine was examd. in the presence of 2 kinds of .alpha.2-antagonists: agents that label imidazoline receptors and exert a pharmacol. action through imidazoline receptors (idazoxan and atipamezole) and agents that are nonimidazoline compds. and are lacking in pharmacol. action through imidazoline receptors (rauwolscine and L-659,066). They were given intracerebroventricularly. Idazoxan and atipamezole inhibited the antidysrhythmic action of dexmedetomidine, whereas rauwolscine and L-659,066 did not. Thus, because .alpha.2-antagonists having imidazoline or imidazole structures inhibited the antidysrhythmic action of dexmedetomidine, and the inhibition produced by the nonimidazoline .alpha.2-antagonists was not significant, imidazoline receptors in the central nervous system are more responsible for the antidysrhythmic action of dexmedetomidine than are .alpha.2-adrenoceptors.

IT **104054-27-5**, Atipamezole
RL: **BAC (Biological activity or effector, except adverse)**; BIOL (Biological study)
(dexmedetomidine inhibition of halothane-epinephrine-induced arrhythmias response to)

L64 ANSWER 12 OF 118 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:888340 CAPLUS
DOCUMENT NUMBER: 123:306477
TITLE: Effects of a selective .alpha.2-adrenoceptor antagonist, atipamezole, on hypothalamic histamine and noradrenaline release in vivo
AUTHOR(S): Laitinen, Kirsti S. M.; Tuomisto, Leena; MacDonald, Ewen
CORPORATE SOURCE: Department of Pharmacology and Toxicology, University of Kuopio, P.O.B. 1627, Kuopio, FIN-70211, Finland
SOURCE: Eur. J. Pharmacol. (1995), 285(3), 255-60
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In vivo microdialysis was used to study the effects of a potent and selective .alpha.2-adrenoceptor antagonist, atipamezole, on histamine and noradrenaline release from the medial hypothalamus in anesthetized rats. Local perfusion with atipamezole via the microdialysis probe increased histamine release significantly and dose-dependently. However, the effect of systemic administration of atipamezole (1 mg/kg) was the opposite in that it significantly decreased histamine release. Local and systemic administration of atipamezole produced an approx. 2-fold increase in noradrenaline release. To study the modulatory effect of noradrenergic neurons on histamine release, noradrenaline synthesis was inhibited with .alpha.-methyl-p-tyrosine. In the microdialysis expt., rats that received .alpha.-methyl-p-tyrosine exhibited no decrease, but rather a slight increase in histamine release in response to systemic atipamezole administration. These results show clearly that atipamezole enhances noradrenaline release in vivo from rat hypothalamus and its effects on

histamine release are dependent on the route of drug administration.
IT **104054-27-5**, Atipamezole
RL: **BAC (Biological activity or effector, except adverse)**; BIOL (Biological study)
(effects of selective .alpha.2-adrenoceptor antagonist atipamezole on hypothalamic histamine and noradrenaline release in vivo)

L64 ANSWER 13 OF 118 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:888338 CAPLUS
DOCUMENT NUMBER: 123:306476
TITLE: Effect of .alpha.2-adrenergic drugs dexmedetomidine and atipamezole on extracellular amino acid levels in vivo
AUTHOR(S): Valtonen, Pirjo; Haapalinna, Antti; Riekkinen, Sr., Paavo; Halonen, Toivo
CORPORATE SOURCE: A.I. Virtanen Institute and Department of Neurology, University of Kuopio, Kuopio, Finland
SOURCE: Eur. J. Pharmacol. (1995), 285(3), 239-46
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
AB .alpha.2-Adrenoceptors are known to be involved in a variety of physiol. functions and pathol. conditions, including epilepsy and the extent of excitotoxin-induced cell death. In this study the authors evaluated whether selective .alpha.2-adrenergic drugs can modulate the release of neurotransmitter amino acids. The effect of the .alpha.2-adrenoceptor agonist dexmedetomidine (5 .mu.g/kg, s.c.) and the .alpha.2-adrenoceptor antagonist atipamezole (0.1 mg/kg and 1 mg/kg, s.c.) on the release of extracellular glutamate, aspartate and .gamma.-aminobutyric acid (GABA) was studied with microdialysis in the hippocampus of freely moving rats under basal and K+-evoked conditions. Atipamezole (1 mg/kg) decreased K+-evoked glutamate efflux by 30% compared to the control group but did not affect significantly the effluxes of aspartate and GABA. Dexmedetomidine and the lower dose of atipamezole (0.1 mg/kg) did not significantly alter the evoked overflow of amino acids. The results suggest that .alpha.2-adrenergic drugs have only modest effects on the K+-stimulated overflow of extracellular neurotransmitter amino acids in rat hippocampus.
IT **104054-27-5**, Atipamezole
RL: **BAC (Biological activity or effector, except adverse)**; BIOL (Biological study)
(effect of .alpha.2-adrenergic drugs dexmedetomidine and atipamezole on extracellular amino acid levels in vivo in hippocampus)

L64 ANSWER 14 OF 118 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:877552 CAPLUS
DOCUMENT NUMBER: 123:306528
TITLE: Nonadrenergic binding of [3H]atipamezole in rat lung: A novel imidazole binding site?
AUTHOR(S): Sjoholm, Birgitta; Savola, Juha-Matti; Scheinin, Mika
CORPORATE SOURCE: Department Pharmacology, University Turku, Turku, FIN-20101, Finland
SOURCE: Ann. N. Y. Acad. Sci. (1995), 763(Imidazoline Receptor: Pharmacology, Functions, Ligands, and Relevance to Biology and Medicine), 66-77
CODEN: ANYAA9; ISSN: 0077-8923
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study characterized the nonadrenergic binding of [3H]atipamezole in rat lung as a possible imidazole binding site.
IT **104054-27-5**, Atipamezole
RL: **BAC (Biological activity or effector, except adverse)**; BPR (Biological process); BIOL (Biological study); PROC (Process)

(nonadrenergic binding of atipamezole in lung)

L64 ANSWER 15 OF 118 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:714770 CAPLUS
DOCUMENT NUMBER: 123:160640
TITLE: Influence of selective .alpha.2-adrenergic agents on mustard oil-induced central hyperalgesia in rats
AUTHOR(S): Mansikka, Heikki; Pertovaara, Antti
CORPORATE SOURCE: Department of Physiology, University of Helsinki, Helsinki, Finland
SOURCE: Eur. J. Pharmacol. (1995), 281(1), 43-8
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of systemically administered medetomidine, an .alpha.2-adrenoceptor agonist, and atipamezole, an .alpha.2-adrenoceptor antagonist, on mustard oil-induced central hyperalgesia were detd. in unanesthetized rats. The mech. threshold for eliciting a hindlimb flexion reflex (a nocifensive response) was detd. with a series of calibrated monofilaments. Under control conditions mustard oil produced a significant decrease of the hindlimb withdrawal threshold for mech. stimuli applied to a distal site in the hindlimb, whereas the corresponding threshold in the (untreated) contralateral side was not changed. Medetomidine administered 12 min prior to mustard oil treatment produced a significant dose-dependent (3-30 .mu.g/kg s.c.) attenuation of the mustard oil-induced threshold decrease whereas the withdrawal threshold of the contralateral (untreated) hindlimb was not changed at these low doses. The antinociceptive effect of medetomidine (10 .mu.g/kg) administered 12 min prior to the mustard oil treatment was not significantly stronger than the effect of medetomidine administered immediately after the mustard oil treatment. Atipamezole at a high (1000 .mu.g/kg) or a low (10 .mu.g/kg) dose did not influence the mustard oil-induced threshold decrease, whereas at an intermediate dose (100 .mu.g/kg) atipamezole alone had a significant antinociceptive effect on mustard oil-induced hyperalgesia. The results indicate that medetomidine produces a selective attenuation of central hyperalgesia at doses which are sub-antinociceptive in intact rats. A pre-emptive treatment with medetomidine did not produce stronger antinociception than medetomidine treatment after the development of hyperalgesia. An .alpha.2-adrenoceptor antagonist, atipamezole, attenuated central hyperalgesia in a non-monotonic fashion.

IT **104054-27-5**, Atipamezole
RL: **BAC (Biological activity or effector, except adverse)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(medetomidine and atipamezole, .alpha.2-adrenergic agents, antinociceptive activity)

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L114         80 SEA FILE=MEDLINE ABB=ON  GUANOXAN#
L117      17840 SEA FILE=MEDLINE ABB=ON  ANALGESIA+NT/CT
L118      18425 SEA FILE=MEDLINE ABB=ON  ANALGESICS/CT
L119       8724 SEA FILE=MEDLINE ABB=ON  "HYPNOTICS AND SEDATIVES"/CT
L120        615 SEA FILE=MEDLINE ABB=ON  (L105 OR L106 OR L107 OR L108 OR L109
               OR L110 OR L111 OR L112 OR L113 OR L114) AND (L117 OR L118 OR
               L119)
L122      36479 SEA FILE=MEDLINE ABB=ON  HORSES/CT
L127          2 SEA FILE=MEDLINE ABB=ON  L122 AND L120



L210         36 L121 OR L126 OR L127

=> fil embase; d que l167; d que l171; d que l173; d que l175
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L136      23010 SEA FILE=EMBASE ABB=ON  GUANABENZ/CT OR GUANABENZ ACETATE/CT
               OR GUANOXABENZ/CT OR CLONIDINE/CT OR CLONIDINE DERIVATIVE/CT
L137       7633 SEA FILE=EMBASE ABB=ON  GUANACLINE/CT OR GUANADREL/CT OR
               GUANAZODINE/CT OR GUANETHIDINE/CT OR GUANFACINE/CT OR GUANOCLOR
               /CT
L138        200 SEA FILE=EMBASE ABB=ON  GUANOXAN/CT
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L142 36020 SEA FILE=EMBASE ABB=ON ANALGESIA+NT/CT
L143 13092 SEA FILE=EMBASE ABB=ON SEDATION/CT
L144 906 SEA FILE=EMBASE ABB=ON HYPNOTIC SEDATIVE AGENT/CT
L145 17921 SEA FILE=EMBASE ABB=ON ANALGESIC AGENT/CT
L146 10377 SEA FILE=EMBASE ABB=ON HORSE/CT
L147 339127 SEA FILE=EMBASE ABB=ON DOG/CT OR CAT/CT OR CATTLE/CT OR GOAT/CT OR SWINE/CT OR SHEEP/CT OR L146
L148 2053 SEA FILE=EMBASE ABB=ON (L136 OR L137 OR L138) AND (L142 OR L143 OR L144 OR L145)
L166 411 SEA FILE=EMBASE ABB=ON L148 AND GENERAL REVIEW/DT
L167 1 SEA FILE=EMBASE ABB=ON L147 AND L166

L136 23010 SEA FILE=EMBASE ABB=ON GUANABENZ/CT OR GUANABENZ ACETATE/CT OR GUANOXABENZ/CT OR CLONIDINE/CT OR CLONIDINE DERIVATIVE/CT
L137 7633 SEA FILE=EMBASE ABB=ON GUANACLINE/CT OR GUANADREL/CT OR GUANAZODINE/CT OR GUANETHIDINE/CT OR GUANFACINE/CT OR GUANOCLOR/CT
L138 200 SEA FILE=EMBASE ABB=ON GUANOXAN/CT
L142 36020 SEA FILE=EMBASE ABB=ON ANALGESIA+NT/CT
L143 13092 SEA FILE=EMBASE ABB=ON SEDATION/CT
L144 906 SEA FILE=EMBASE ABB=ON HYPNOTIC SEDATIVE AGENT/CT
L145 17921 SEA FILE=EMBASE ABB=ON ANALGESIC AGENT/CT
L160 19399 SEA FILE=EMBASE ABB=ON L136/MAJ OR L137/MAJ OR L138/MAJ
L161 40879 SEA FILE=EMBASE ABB=ON L142/MAJ OR L143/MAJ OR L144/MAJ OR L145/MAJ
L162 861 SEA FILE=EMBASE ABB=ON L160 AND L161
L170 38 SEA FILE=EMBASE ABB=ON L162 AND GENERAL REVIEW/DT
L171 4 SEA FILE=EMBASE ABB=ON L170 NOT CLONIDINE/CT

L136 23010 SEA FILE=EMBASE ABB=ON GUANABENZ/CT OR GUANABENZ ACETATE/CT OR GUANOXABENZ/CT OR CLONIDINE/CT OR CLONIDINE DERIVATIVE/CT
L137 7633 SEA FILE=EMBASE ABB=ON GUANACLINE/CT OR GUANADREL/CT OR GUANAZODINE/CT OR GUANETHIDINE/CT OR GUANFACINE/CT OR GUANOCLOR/CT
L138 200 SEA FILE=EMBASE ABB=ON GUANOXAN/CT
L142 36020 SEA FILE=EMBASE ABB=ON ANALGESIA+NT/CT
L143 13092 SEA FILE=EMBASE ABB=ON SEDATION/CT
L144 906 SEA FILE=EMBASE ABB=ON HYPNOTIC SEDATIVE AGENT/CT
L145 17921 SEA FILE=EMBASE ABB=ON ANALGESIC AGENT/CT
L146 10377 SEA FILE=EMBASE ABB=ON HORSE/CT
L147 339127 SEA FILE=EMBASE ABB=ON DOG/CT OR CAT/CT OR CATTLE/CT OR GOAT/CT OR SWINE/CT OR SHEEP/CT OR L146
L160 19399 SEA FILE=EMBASE ABB=ON L136/MAJ OR L137/MAJ OR L138/MAJ
L161 40879 SEA FILE=EMBASE ABB=ON L142/MAJ OR L143/MAJ OR L144/MAJ OR L145/MAJ
L162 861 SEA FILE=EMBASE ABB=ON L160 AND L161
L172 86 SEA FILE=EMBASE ABB=ON L162 NOT CLONIDINE/CT
L173 2 SEA FILE=EMBASE ABB=ON L172 AND L147

L136 23010 SEA FILE=EMBASE ABB=ON GUANABENZ/CT OR GUANABENZ ACETATE/CT OR GUANOXABENZ/CT OR CLONIDINE/CT OR CLONIDINE DERIVATIVE/CT
L137 7633 SEA FILE=EMBASE ABB=ON GUANACLINE/CT OR GUANADREL/CT OR GUANAZODINE/CT OR GUANETHIDINE/CT OR GUANFACINE/CT OR GUANOCLOR/CT
L138 200 SEA FILE=EMBASE ABB=ON GUANOXAN/CT
L142 36020 SEA FILE=EMBASE ABB=ON ANALGESIA+NT/CT
L143 13092 SEA FILE=EMBASE ABB=ON SEDATION/CT

```
L144        906 SEA FILE=EMBASE ABB=ON  HYPNOTIC SEDATIVE AGENT/CT
L145      17921 SEA FILE=EMBASE ABB=ON  ANALGESIC AGENT/CT
L160      19399 SEA FILE=EMBASE ABB=ON  L136/MAJ OR L137/MAJ OR L138/MAJ
L161      40879 SEA FILE=EMBASE ABB=ON  L142/MAJ OR L143/MAJ OR L144/MAJ OR
                L145/MAJ
L162        861 SEA FILE=EMBASE ABB=ON  L160 AND L161
L170         38 SEA FILE=EMBASE ABB=ON  L162 AND GENERAL REVIEW/DT
L174        113 SEA FILE=EMBASE ABB=ON  (L142 OR L145) AND (L143 OR L144) AND
                L160
L175          7 SEA FILE=EMBASE ABB=ON  L170 AND L174


=> s l167 or l171 or l173 or l175
L211         14 L167 OR L171 OR L173 OR L175

=> fil embase; d que l189; d que l192; d que l195
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L176         23 SEA FILE=WPIDS ABB=ON  GUANABENZ OR BR 750 OR WY 8678 OR
                WYTENSIN
L177        261 SEA FILE=WPIDS ABB=ON  CLONIDIN# OR CHLONIDIN# OR ST 155
L178          2 SEA FILE=WPIDS ABB=ON  GUANOXABENZ OR HYDROXYGUANABENZ
L179          0 SEA FILE=WPIDS ABB=ON  GUANACLIN# OR CYCLAZENIN#
L180          4 SEA FILE=WPIDS ABB=ON  GUANADREL OR GUANAZODIN# OR SANEG!T OR
                GUANOCLOR OR GUANOCHLOR? OR GUANOXAN#
L181         49 SEA FILE=WPIDS ABB=ON  GUANETHIDIN# OR ISMELIN# OR O!TADIN# OR
                GUANFACIN# OR ESTULIC
L183       5594 SEA FILE=WPIDS ABB=ON  SEDAT?
L184      17932 SEA FILE=WPIDS ABB=ON  ANALGES?
L185         64 SEA FILE=WPIDS ABB=ON  (L176 OR L177 OR L178 OR L179 OR L180
                OR L181) AND (L183 OR L184)
L186       8814 SEA FILE=WPIDS ABB=ON  HORSE# OR EQUINE
L187      58642 SEA FILE=WPIDS ABB=ON  DOG# OR CANINE OR CAT# OR FELINE OR
                CATTLE OR COW# OR GOAT# OR CAPRINE OR SWINE OR HOG# OR PIG# OR
                PORCINE OR OVINE OR SHEEP
L189          0 SEA FILE=WPIDS ABB=ON  L185 AND (L186 OR L187)



L176         23 SEA FILE=WPIDS ABB=ON  GUANABENZ OR BR 750 OR WY 8678 OR
                WYTENSIN
L177        261 SEA FILE=WPIDS ABB=ON  CLONIDIN# OR CHLONIDIN# OR ST 155
L178          2 SEA FILE=WPIDS ABB=ON  GUANOXABENZ OR HYDROXYGUANABENZ
L179          0 SEA FILE=WPIDS ABB=ON  GUANACLIN# OR CYCLAZENIN#
L180          4 SEA FILE=WPIDS ABB=ON  GUANADREL OR GUANAZODIN# OR SANEG!T OR
                GUANOCLOR OR GUANOCHLOR? OR GUANOXAN#
L181         49 SEA FILE=WPIDS ABB=ON  GUANETHIDIN# OR ISMELIN# OR O!TADIN# OR
                GUANFACIN# OR ESTULIC
L183       5594 SEA FILE=WPIDS ABB=ON  SEDAT?
L184      17932 SEA FILE=WPIDS ABB=ON  ANALGES?
L185         64 SEA FILE=WPIDS ABB=ON  (L176 OR L177 OR L178 OR L179 OR L180
                OR L181) AND (L183 OR L184)
L191       9083 SEA FILE=WPIDS ABB=ON  VETERIN?
L192          0 SEA FILE=WPIDS ABB=ON  L185 AND L191
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L176          23 SEA FILE=WPIDS ABB=ON  GUANABENZ OR BR 750 OR WY 8678 OR
                 WYTENSIN
L177         261 SEA FILE=WPIDS ABB=ON  CLONIDIN# OR CHLONIDIN# OR ST 155
L178           2 SEA FILE=WPIDS ABB=ON  GUANOXABENZ OR HYDROXYGUANABENZ
L179           0 SEA FILE=WPIDS ABB=ON  GUANACLIN# OR CYCLAZENIN#
L180           4 SEA FILE=WPIDS ABB=ON  GUANADREL OR GUANAZODIN# OR SANEG!T OR
                 GUANOCLOR OR GUANOCHLOR? OR GUANOXAN#
L181          49 SEA FILE=WPIDS ABB=ON  GUANETHIDIN# OR ISMELIN# OR O!TADIN# OR
                 GUANFACIN# OR ESTULIC
L183        5594 SEA FILE=WPIDS ABB=ON  SEDAT?
L184       17932 SEA FILE=WPIDS ABB=ON  ANALGES?
L190          21 SEA FILE=WPIDS ABB=ON  L183 AND L184 AND (L176 OR L177 OR L178
                 OR L179 OR L180 OR L181)
L193          21 SEA FILE=WPIDS ABB=ON  L183(15A)((L176 OR L177 OR L178 OR L179
                 OR L180 OR L181))
L194          11 SEA FILE=WPIDS ABB=ON  L184(15A)((L176 OR L177 OR L178 OR L179
                 OR L180 OR L181))
L195          11 SEA FILE=WPIDS ABB=ON  L190 AND (L193 OR L194)


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=> d que l206
L1             1 SEA FILE=REGISTRY ABB=ON  GUANABENZ/CN
L2             1 SEA FILE=REGISTRY ABB=ON  "GUANABENZ ACETATE"/CN
L3             1 SEA FILE=REGISTRY ABB=ON  GUANOXABENZ/CN
L8             1 SEA FILE=REGISTRY ABB=ON  GUANACLINE/CN
L13            1 SEA FILE=REGISTRY ABB=ON  GUANADREL/CN
L20            1 SEA FILE=REGISTRY ABB=ON  GUANAZODINE/CN
L25            1 SEA FILE=REGISTRY ABB=ON  GUANETHIDINE/CN
L26            1 SEA FILE=REGISTRY ABB=ON  GUANFACINE/CN
L27            1 SEA FILE=REGISTRY ABB=ON  GUANOCLOR/CN
L32            1 SEA FILE=REGISTRY ABB=ON  GUANOXAN/CN
L37            1 SEA FILE=REGISTRY ABB=ON  4205-90-7
L176          23 SEA FILE=WPIDS ABB=ON  GUANABENZ OR BR 750 OR WY 8678 OR
                 WYTENSIN
L177         261 SEA FILE=WPIDS ABB=ON  CLONIDIN# OR CHLONIDIN# OR ST 155
L178           2 SEA FILE=WPIDS ABB=ON  GUANOXABENZ OR HYDROXYGUANABENZ
L179           0 SEA FILE=WPIDS ABB=ON  GUANACLIN# OR CYCLAZENIN#
L180           4 SEA FILE=WPIDS ABB=ON  GUANADREL OR GUANAZODIN# OR SANEG!T OR
                 GUANOCLOR OR GUANOCHLOR? OR GUANOXAN#
L181          49 SEA FILE=WPIDS ABB=ON  GUANETHIDIN# OR ISMELIN# OR O!TADIN# OR
                 GUANFACIN# OR ESTULIC
L199      145539 SEA HORSE# OR EQUINE
L200       13905 SEA L1 OR L2 OR L3 OR L37 OR L8 OR L13 OR L20 OR L25 OR L26 OR
                 L27 OR L32 OR L37
L201       17827 SEA (L176 OR L177 OR L178 OR L179 OR L180 OR L181)
L204       62532 SEA ANALGES?
L205       18817 SEA SEDAT?
L206           8 SEA (L200 OR L201) AND L199 AND (L204 OR L205)


=> dup rem l210,l206,l209,l211,l195
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PROCESSING COMPLETED FOR L210
PROCESSING COMPLETED FOR L206
PROCESSING COMPLETED FOR L209
PROCESSING COMPLETED FOR L211
PROCESSING COMPLETED FOR L195
L212 83 DUP REM L210 L206 L209 L211 L195 (9 DUPLICATES REMOVED)
ANSWERS '1-36' FROM FILE MEDLINE
ANSWERS '37-38' FROM FILE AGRICOLA
ANSWERS '39-58' FROM FILE CAPLUS
ANSWERS '59-72' FROM FILE EMBASE
ANSWERS '73-83' FROM FILE WPIDS

=> sort l212 py a 1-
PROCESSING COMPLETED FOR L212
L213 83 SORT L212 1- PY A

=> d ibib ab hitrn 1-40 — oldest 40 answers

L213 ANSWER 1 OF 83 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1987-112962 [16] WPIDS
DOC. NO. CPI: C1987-047132
TITLE: Medical poultice with improved dermal absorption - contains glycerol tri ester dermal absorption accelerator, as well as polymeric base material.
DERWENT CLASS: A96 B05 B07 D22
PATENT ASSIGNEE(S): (NITL) NITTO ELECTRIC IND CO
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
JP 62059224	A	19870314	(198716)*		6

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
JP 62059224	A	JP 1985-199269	19850909

PRIORITY APPLN. INFO: JP 1985-199269 19850909
AB JP 62059224 A UPAB: 19930922
Medical poultice is obtd. by sealing a base material comprising polymers

and a medical component contg. a dermal absorption accelerator of formula (I) over a support.

Pref. the polymers are acrylic polymer such as n-butyl(meth)acrylate, 2-ethylbutylacrylate, isooctylacrylate, (2-ethyl)hexylacrylate, etc. or a copolymer of the acrylic acid ester and a monomer (e.g. (metha)acrylic acid, itaconic acid, maleic acid, hydroxyethylacrylate, acrylamide, vinylacetate, etc.) The medical component is corticosteroid (e.g. hydrocortisone, prednisolone, beclomethasone propionate, etc.); **analgesic** anitinflamatories (e.g. acetoaminophene, mefenamic acid, indomethacin, etc.); hypnotic **sedative** (e.g. nitrazepan, lorazepam, etc.); tranquilisers (e.g. fluphenazine, diazepam, etc.); antihypertensives (e.g. **clonidine**, pindolol, nimodipine, nifedipine, etc.); etc. The support includes a soft material made from polyester, polyurethane, PVA, polyamide, etc. Combined ratio of the polymer, medical component and the accelerator is 20-100 wt.pts., 0.01-20 and 5-50.

USE/ADVANTAGE - Due to the addition of the accelerator, dermal absorption of the medical component is improved.

0/0

L213 ANSWER 2 OF 83 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1989-042235 [06] WPIDS
DOC. NO. CPI: C1989-018519
TITLE: External adhesives - comprises drug, high molecular basic layer contg. propyl gallate as drug stabiliser and adhesive laminated to support.
DERWENT CLASS: A96 B07 D22
PATENT ASSIGNEE(S): (NITL) NITTO ELECTRIC IND CO
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
JP 63313723	A	19881221	(198906)*		7

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
JP 63313723	A	JP 1987-149509	19870616

PRIORITY APPLN. INFO: JP 1987-149509 19870616

AB JP 63313723 A UPAB: 19930923

External adhesives on which a drug, high molecular basic layer contg. propyl gallate as stabiliser for drug, and pressure-sensitive adhesive are laminated to a support in this order. The distribution rate of propyl gallate to the pressure-sensitive adhesive layer is smaller than that of the high molecular basic layer, i.e. 0.3 or lower.

The pressure-sensitive adhesive includes single polymers of (meth)acrylates (acrylic adhesives), e.g. butyl (meth)acrylate or their copolymers with a monomer, e.g. (meth)acrylic acid, maleic acid, itaconic acid; lipophilic high molecular cpds., e.g. silicon adhesive, polyisoprene rubber. The drug applicable to the adhesives includes corticosteroids (e.g. hydrocortisone, prednisolone), **analgesic** antiinflammatory agents (e.g. acetaminophene, mefenamic acid, flufenamic acid), hypnotic **sedatives** (e.g. phenobarbital, triazolam, nitrazepam), tranquillisers (e.g. fluphenazine, diazepam, haloperidol), antihypertensives (e.g. **clonidine**, pindolol, propanolol, idenolol), diuretics (e.g. hydrothiazide), antibiotics (e.g. penicillin, tetracyclin, fradiomycin, erythromycin), anaesthetics (e.g. lidocaine), bactericidal agents (e.g. nitrofurazone), antifungal agents (e.g. pentamycin, nystatin), etc. The content in the adhesives is fixed at

0.01-30 wt.%, pref. 0.2-20 wt.%. Propyl gallate may be added in amt. 1.0-5 wt.%, pref. 1.0-3 wt.%, for the whole adhesives. The pref. support is laminate films comprising aluminium thin film and plastic film.

USE/ADVANTAGE - Use of propyl gallate is effective in increasing stability of the drug contained over a long period of time. The skin-irritation property of propyl gallate is decreased by inhibiting release of it with the pressure-sensitive adhesive. The drug is absorbed well into the living body.

0/0

L213 ANSWER 3 OF 83 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1990-018131 [03] WPIDS
DOC. NO. NON-CPI: N1990-013884
DOC. NO. CPI: C1990-007735
TITLE: Adhesive compsn. for surgical tape - comprises A-B-A type block copolymer, alicyclic petroleum resin, softening agent and water absorbing polymer.
DERWENT CLASS: A96 B07 D22 G03 P34
PATENT ASSIGNEE(S): (HISM) HISAMITSU PHARM CO LTD
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
JP 01297069	A	19891130	(199003)*		7
JP 07036835	B2	19950426	(199521)		5

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
JP 01297069	A	JP 1988-129387	19880525
JP 07036835	B2	JP 1988-129387	19880525

FILING DETAILS:

PATENT NO	KIND		PATENT NO
JP 07036835	B2	Based on	JP 01297069

PRIORITY APPLN. INFO: JP 1988-129387 19880525
AB JP 01297069 A UPAB: 19930928
Adhesive compsn. comprises (1) 10-30 wt.pts. A-B-A type block copolymer, (2) 10-50 wt.pts. alicyclic petroleum resin, (3) 10-50 wt.pts. softening agent, and (4) 1-10 wt.pts. water-absorbing polymer.

The block copolymer pref. comprises monovinyl substd. aromatic cpd. A and conjugated diolefin copolymer B, including ''Kaliflex-TR-1101'' or ''TR-1107''. The water-absorbing polymer is at least one of water-soluble polymers, including ''Sun wet-IM-300'' or ''IM-300 MPS''. The softening agent is higher fatty acid, liquified rubber or mineral oil. The resin is ''Arcon-P-85'' or ''P-100''(RTM). The compsn. opt. contains medicated components e.g. **analgesic** anti-inflammatories e.g. salicylic acid, methylsalicylate, l-methol, camphor, indomethacin, ketoprofen or diclofenac sodium; hypnotic **sedatives** e.g. nitrazepam, lorazepam or diazepam; antihypertensives e.g. **clonidine**, or pindolol; coronary dilator e.g. nitroglycerin, or isosorbide dinitrate; antitussives e.g. ephedrine hydrochloride; antihistamines e.g. diphenyhydroamine hydrochloride or chlor pheniramine maleate); or corticosteroids e.g. hydrocortisone, prednisolone or betamethasone.

USE/ADVANTAGE - Compsns. have good fitness to skin and are useful for surgical tape or therapeutic plasters.

0/0

L213 ANSWER 4 OF 83 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1990-018130 [03] WPIDS
DOC. NO. NON-CPI: N1990-013883
DOC. NO. CPI: C1990-007734
TITLE: Therapeutic adhesive e.g. tape or sheet - comprises polymer obtd. by polymerising unsatd. monomer with phenoxy-poly-alkylene-glycol residue, on film of polyethylene.
DERWENT CLASS: A96 B07 D22 P34
PATENT ASSIGNEE(S): (NITL) NITTO DENKO CORP
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
JP 01297068	A	19891130	(199003)*		7

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
JP 01297068	A	JP 1988-129359	19880525

PRIORITY APPLN. INFO: JP 1988-129359 19880525
AB JP 01297068 A UPAB: 19930928
Therapeutic adhesive, comprises polymer obtd. with polymerisation of 10 wt.% or more of unsatd. monomer contg. at side chain phenoxypoly-alkyleneglycol residue or alkylphenoxy polyalkyleneglycol. Pref. unsatd. monomer is of formula X-Y-Z (X is residue contg. unsatd. double bond e.g. vinyl or (meth)acr-yloyl; Y is polyalkylene glycol residue and Z is phenyl or alkylphenyl), including (meth)acrylic acid phenoxytetra ethylene- or (meth)acrylic acid phenoxypolyethylene glycolester, (meth)acrylic acid phenoxypolypropyleneglycol, (meth)acrylic acid nonylphenoxy diethylene- or (meth)acrylic acid nonylphenoxypolypropylene glycol ester. Therapeutic adhesive is coated over film of sheet of polyethylene, polyester, poly(ethylene/vinylacetate), polyurethane, paper or metal foil with thickness of 10-1000 micro-m. Adhesive can contain medicated component, e.g.
corticosteroids (e.g. hydrocortisone, prednisolone or triamcinolone); **analgesic** antiinflammatories (e.g. acetoaminophene, mefenamic acid or indomethacin); hypnotic **sedatives** (e.g. phenobarbital, amobarbital or lorazepam); tranquillisers (e.g. fluphenazine or diazepam); antihypertensives (e.g. **clonidine**, pindolol or indenolol); hypotensive diuretics (e.g. hydrothiazide); antibiotics (e.g. penicillin or tetracyclin); or antiepilepsy (e.g. nitrrazepam or meprobamate).
USE/ADVANTAGE - For therapeutic adhesive e.g. tape or sheet.
0/0

L213 ANSWER 5 OF 83 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1990-294277 [39] WPIDS
DOC. NO. CPI: C1990-126937
TITLE: Percutaneous compsns. - contg. a medicated substance and limonene.
DERWENT CLASS: B05 B07
INVENTOR(S): NAGAI, T; OKABE, H; TAKAYAMA, K
PATENT ASSIGNEE(S): (FSKF-N) FSK KK; (LINT-N) LINTEC CORP
COUNTRY COUNT: 2
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
JP 02207024	A	19900816	(199039)*		

US 5164416	A	19921117 (199249)	12
JP 2651616	B2	19970910 (199741)	7

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
JP 02207024	A		JP 1989-26322	19890203
US 5164416	A	CIP of	US 1990-471863	19900129
			US 1991-700046	19910508
JP 2651616	B2		JP 1989-26322	19890203

FILING DETAILS:

PATENT NO	KIND		PATENT NO
JP 2651616	B2	Previous Publ.	JP 02207024

PRIORITY APPLN. INFO: JP 1989-26322 19890203

AB JP 02207024 A UPAB: 19930928
A percutaneous prepn. contg. (1) a medicated substance, and (2) 0.1-30 wt.% (based on the total percutaneous prepn.) of limonene, is new. Pref. limonene is d-limonene. The medicated substance is corticosteroid (e.g. prednisolone, dexamethasone, hydrocortisone or fluocinolone acetonide); antiinflammatory (e.g. indomethacin, diclofenac, ibuprofen, ketoprofen, flufenamic acid or methyl salicylate); antihistamine (e.g. diphenhydramine, chlorpheniramine); hypnotic **sedative** (e.g. nitrazepam, diazepam or phenobarbital); hormone (e.g. insulin, or testosterone); antihypertensive (e.g. **clonidine**, propranolol hydrochloride, pindolol or procaine imide hydrochloride); coronary dilator (e.g. nitroglycerin, isosorbide nitrate, or nifedipine); anaesthetic (e.g. lidocaine, or benzocaine); hypnotics (e.g. cyclobarbital or phenobarbital); **analgesic** (e.g. morphine or acetoanilide); antibiotic (e.g. penicillin, tetracyclin, or erythromycin); antibacterial (e.g. benzalconium hydrochloride or acetophenyl amine); diuretic (e.g. hydrochloro thiazide); etc.
USE/ADVANTAGE - Percutaneous prepn. with safety and good percutaneous ability. @
0/0

L213 ANSWER 6 OF 83 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1992-258996 [31] WPIDS
CROSS REFERENCE: 1993-272191 [34]
DOC. NO. CPI: C1992-115476
TITLE: Amino-2-imidazoline derivs. prodn., used as hypotensives, **sedatives**, etc. - by reacting imidazoline sulphonic acid with prim. or sec. amine in liq. medium contg. at least one alcohol.
DERWENT CLASS: B03
INVENTOR(S): GLUCHOWSKI, C
PATENT ASSIGNEE(S): (ALLR) ALLERGAN INC
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5130441	A	19920714	(199231)*		8

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 5130441	A	US 1990-475842	19900206

PRIORITY APPLN. INFO: US 1990-475842 19900206
AB US 5130441 A UPAB: 19931119
Prodn. of 2-amino-2-imidazolines of formula (II) is effected by reacting an imidazoline sulphonic acid (III) with a prim. or sec. amine, opt. in salt form, in a liq. medium comprising or contg. at least one sec. and/or tert. alcohol (IV). In (I) R1 = opt. substd. hydrocarbyl or heterocyclyl; R2 and R3 = H or opt. substd. hydrocarbyl or heterocyclyl; or R1 and R2 are joined together (sic).
USE - (II), e.g. **clonidine**, are useful as hypotensives, **sedatives**, **analgesics**, agents for treating drug and alcohol withdrawal symptoms, diuretics, antidiarrhoeal agents, agents for lowering intraocular pressure, and vasoconstrictors.
0/0
ct
Dwg.0/0

L213 ANSWER 7 OF 83 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1997-309784 [28] WPIDS
DOC. NO. NON-CPI: N1997-256721
DOC. NO. CPI: C1997-099579
TITLE: Induction of general anaesthesia, profound **sedation**, or **analgesia** - by administering anaesthesia-producing drug to produce amnesia then further administrating **clonidine** and fentanyl to produce surgical anaesthesia.
DERWENT CLASS: B05 B07 P32
INVENTOR(S): GEVIRTZ, C; KATZ, D P; NAGASHIMA, H
PATENT ASSIGNEE(S): (MONT-N) MONTEFIORE MEDICAL CENT
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5635204	A	19970603	(199728)*		5

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 5635204	A	US 1994-205939	19940304

PRIORITY APPLN. INFO: US 1994-205939 19940304
AB US 5635204 A UPAB: 19970709
Induction of surgical anaesthesia in a mammal comprises: (i) transdermally administering, via a transdermal patch, an anaesthesia-producing drug chosen from scopolamine, ketamine and benzodiazepines to produce amnesia; and (ii) after an amnesic state is produced, transdermally administrating **clonidine** and fentanyl to produce surgical anaesthesia. Also claimed are: (a) the induction of **sedation**; and (b) the reversal of surgical anaesthesia.
USE - The method is used to induce surgical anaesthesia (claimed), profound **sedation**, and/or **analgesia**, or in another aspect, the method can be used to reverse anaesthesia.
ADVANTAGE - The method using synergistic agents reduces the total amount of general anaesthetic agent required to produce anaesthetic, and can be performed by paramedics and other emergency personnel who are not physicians. The method allows anaesthesia to be given to patients in whom it is difficult to administer and control inhalational or intravenous anaesthesia.
Dwg.1/2

L213 ANSWER 8 OF 83 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1997-332564 [30] WPIDS
DOC. NO. NON-CPI: N1997-276040
DOC. NO. CPI: C1997-106696
TITLE: Self administration drug delivery apparatus - comprises housing for cartridge attached to skin with delivery needle to penetrate skin when housing is pushed against the base.
DERWENT CLASS: B07 P34
INVENTOR(S): GROSS, J; LAVI, G; TSALS, I
PATENT ASSIGNEE(S): (ELAN-N) ELAN MEDICAL TECHNOLOGIES LTD; (ELAN-N) ELAN CORP PLC
COUNTRY COUNT: 61
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9721457	A1	19970619	(199730)*	EN	46
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG					
W: AL AU BB BG BR CA CN CZ EE GE HU IL IS JP KP KR LK LT LV MK MX NO NZ PL RO SG SI SK TR TT UA US VN					
ZA 9610374	A	19970827	(199740)		43
AU 9718087	A	19970703	(199743)		
TW 317503	A	19971011	(199807)		
US 5858001	A	19990112	(199910)		
EP 902696	A1	19990324	(199916)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
JP 2000515394 W		20001121	(200064)		45

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9721457	A1		WO 1996-IE85	19961211
ZA 9610374	A		ZA 1996-10374	19961210
AU 9718087	A		AU 1997-18087	19961211
TW 317503	A		TW 1997-101675	19970211
US 5858001	A	Provisional	US 1995-8499	19951211
			US 1996-763311	19961210
EP 902696	A1		EP 1996-945772	19961211
			WO 1996-IE85	19961211
JP 2000515394 W			WO 1996-IE85	19961211
			JP 1997-521904	19961211

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9718087	A	Based on	WO 9721457
EP 902696	A1	Based on	WO 9721457
JP 2000515394 W		Based on	WO 9721457

PRIORITY APPLN. INFO: US 1995-8499 19951211; US 1996-763311 19961210

AB WO 9721457 A UPAB: 19970723
The apparatus (40) to administer a liquid pharmaceutical, contained within a cartridge, is held at the skin through an adhesive at the contact surface (50) on the base (49). The cartridge (48), containing the liquid pharmaceutical, is held within a housing attached to the base (49), so that its longitudinal axis is parallel to the skin contact surface (50). A needle, connected to the supply cartridge (48), penetrates the skin when

the housing is pushed down in relation to the base (49) and also trips a gas generator of citric acid (42) and sodium bicarbonate (43). The gas generator operation moves a piston (41) within the cartridge (48) to compress the drug compartment. The compression forces a channel through the stopper, linking the needle, for the pharmaceutical to be ejected through the needle into the subcutaneous tissue of the patient.

USE - The apparatus is used for the administration of drugs to a patient by subcutaneous, intravenous, intramuscular or intradermal delivery. The pharmaceuticals can be peptides, proteins or hormones such as insulin, calcitonin, cacitonin gene regulating protein, atrial natriuretic protein colony stimulating factor, betaseron, erythropoietin (EPO), interferons such as a, b or g interferon, somatropin, somatostatin, somatomedins, luteinising hormone release hormone (LHRH), tissue plasminogen activator (TPA), growth hormone releasing hormone (GHRH), oxytocin, estradiol, growth hormones, leuprolide acetate, factor VIII, interleukins e.g. interleukin-2 and the like; **analgesics** e.g. fentanyl, sufentanil, butorphanol, buprenorphine, levorphanol, morphine, hydromorphone, hydrocodone, oxymorphone, methodone, lidocaine, bupivacaine, diclofenac, naproxen, paverin; anti-migraine agents e.g. sumatriptan, ergot alkaloids; anti-coagulants e.g. heparin, hirudin; anti-emetics e.g. scopolamine, ondanesetron, domperidone, metoclopramide; cardiovascular agents, anti-hypertensive agents and vasodilators such as diltiazem, **clonidine**, nifedipine, verapamil, isosorbide-5-mononitrate, organic nitrates, agents for the treatment of heart disorders; **sedatives** e.g. benzodiazepines, phenothiozines; narcotic antagonists e.g. naltrexone, naloxone; chelating agents e.g. deferoxamine; anti-diuretics e.g. desmopressin, vasopressin; anti-anginals e.g. nitroglycerine; anti-neoplastics e.g. 5-fluorouracil, bleomycin; prostaglandins; chemotherapy agents e.g. vincristine; and antisense oligonucleotides.

ADVANTAGE - The apparatus gives self-administration of a set dosage of a liquid drug, suitable also for young and elderly patients, without consciously inserting a needle into the skin. The system can be mass produced, for low unit costs.

Dwg.4/21

L213 ANSWER 9 OF 83 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1998-494827 [42] WPIDS
DOC. NO. CPI: C1998-149053
TITLE: Achieving an **analgesic** effect in human, to alleviate chronic neuropathic pain - comprises intraspinal administration of increasing dose of **clonidine** over treatment period, unaccompanied by clinically-adverse haemodynamic effects.
DERWENT CLASS: B03
INVENTOR(S): EDEBURN, P; HASSENBUSCH, S J; TRISSEL, L A
PATENT ASSIGNEE(S): (MEDT) MEDTRONIC INC
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5801188	A	19980901	(199842)*		8

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 5801188	A	US 1997-781030	19970108

PRIORITY APPLN. INFO: US 1997-781030 19970108
AB US 5801188 A UPAB: 19981021

Achieving an **analgesic** effect in a human comprises intraspinal administration of an increasing dose of **clonidine** (I) over a treatment period where the treatment is unaccompanied by clinically-adverse haemodynamic effects. Also claimed are: (A) a method for achieving an **analgesic** effect in a human having a heart beat, comprising: (a) monitoring the heart beat; and (b) administering intraspinally an increasing dose of (I) in a dose responsive to the heart beat to minimise or eliminate bradycardia; and (B) a method for achieving an **analgesic** effect in a human, comprising: (a') implanting in the body, a reservoir of (I) and a delivery system for (I), the delivery system connected to the reservoir; and (b') administering intraspinally, from the reservoir and through the delivery system, an increasing dose of (I), the administration preferably being unaccompanied by adverse haemodynamic or pulmonary effects.

USE - The method is used in the alleviation of chronic neuropathic pain in a human, preferably pain associated with spinal cord injury, plexopathy, diabetic neuropathy, post-herpetic neuralgia, phantom limb pain, stump pain in amputees, peripheral neuropathy, peripheral nerve injury, AIDS neuropathy, reflex sympathetic dystrophy, or primary or metastatic neoplasia (all claimed).

ADVANTAGE - The method avoids the haemodynamic side-effects usually associated with the use of (I), and avoids the use of opiates, such as morphine, which have many negative side effects, e.g. tolerance, toxicity, nausea and vomiting, **sedation**, pruritis and physical dependence.

Dwg.0/3

L213 ANSWER 10 OF 83 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-579551 [49] WPIDS
CROSS REFERENCE: 1996-251532 [25]; 1999-600515 [51]
DOC. NO. CPI: C1999-168540
TITLE: Sustained-release pharmaceutical formulations - provide desired therapeutic effect and sustained-release for 8-24 hours, provide bioavailable, sustained-release oral **analgesia** at reduced daily dose.
DERWENT CLASS: A11 A14 A96 B07
INVENTOR(S): CHASIN, M; HUANG, H; OSHLACK, B
PATENT ASSIGNEE(S): (EURO-N) EUROCELTIQUE SA
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5958452	A	19990928	(199949)*		37

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 5958452	A	CIP of	US 1994-334209	19941104
		CIP of	WO 1995-US14745	19951103
			US 1997-833948	19970410

PRIORITY APPLN. INFO: US 1997-833948 19970410; US 1994-334209 19941104; WO 1995-US14745 19951103

AB US 5958452 A UPAB: 19991210

NOVELTY - Sustained-release pharmaceutical formulations comprising an extruded blend divided into unit doses containing effective amounts of therapeutically active agents to render desired therapeutic effect and provide sustained-release of therapeutically active agent for 8-24 hours.

DETAILED DESCRIPTION - Extruded blend comprises:

(a) therapeutically active agent;

(b) one or more hydrophobic materials chosen from alkylcelluloses,

acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil and/or hydrogenated vegetable oil; and

(c) one or more hydrophobic fusible carriers with melting point of 30-200 deg. C chosen from natural or synthetic waxes, fatty acids, and/or fatty alcohols, and is formed by mixing (a), (b) and (c) in extruder to form blend and extending blend through extruder.

An INDEPENDENT CLAIM is also included for preparation of a sustained-release pharmaceutical extrudate suitable for oral administration.

ACTIVITY - **Analgesic**.

MECHANISM OF ACTION - mu -agonists; mu -antagonists.

USE - Used to provide sustained-release, oral, opioid **analgesia** (claimed). Used to orally deliver opioid **analgesics** including alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, bupernorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dexocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hyromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacyl, morphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone (preferred), oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tramadol and tilidine (claimed). Also used to deliver antihistamines (dimenhydrinate, diphenhydramine, chlorpheniramine, dexchlorpheniramine maleate), **analgesics** (apsirin, codeine, morphine, dihydromorphone, oxycodone), non-steroidal anti-inflammatory drugs (NSAIDs) (naproxen, diclofenac, indomethacin, ibuprofen, sulindac), anti-emetics (metoclopramide, methylnaltrexone), anti-epileptics (phenytoin, meprobamate, nitrazepam), vasodilators (nifedipine, papaverine, diltiazem, nicardipine), antitussive and expectorants (codeine phosphate), anti-asthmatics (theophylline), antacids, antispasmodics (atropine, scopolamine), antidiabetics (insulin), diuretics (ethacrynic acid, bendrofluthiazide), antihypotensives (propranolol, **clonidine**), antihypertensives (**clonidine**, methyldopa), bronchodilators (albuterol), steroids (hydrocortisone, triamcinolone, prednisone), antibiotics (tetracycline), antihemorrhoidals, hypnotics, psychotropics, antidiarrheals, mucolytics, **sedatives**, decongestants, laxatives, vitamins, stimulants (appetite suppressants such as phenylpropanolamine), mixed mu -agonists/antagonists, mu -antagonist combinations.

ADVANTAGE - Bioavailable, sustained-release oral dosage forms, which are easy to produce by melt-extrusion (melt-granulation) technology. They need not be spheronized to obtain final dosage form, and provide increased duration of **analgesic**. **Analgesic** can be administered at a lower daily dose than the prior art while maintaining pain control. Chlorpheniramine maleate controlled-release pellets contained (mg/capsule): chlorpheniramine maleate (60), either ethylcellulose or Eudragit RSPO (RTM: acrylic polymer) as retardant (84) and stearic acid (36). The dissolution of the formulations was tested. The results showed that release rate from ethylcellulose pellets prepared at 105 deg. C was significantly slower than that from Eudragit RSPO (RTM) pellets prepared at 85 deg. C.

DESCRIPTION OF DRAWING(S) - Graph displaying dissolution rates of chlorpheniramine maleate controlled-release pellets containing either ethylcellulose (white circles) or Eudragit RSPO (RTM: acrylic polymer) (black circles) as retardant.

Dwg.1/17

L213 ANSWER 11 OF 83 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

ACCESSION NUMBER: 2001-102801 [11] WPIDS
DOC. NO. CPI: C2001-030139
TITLE: Intraspinal administration of 3-(1-(1H-imdazol-4-yl)-ethyl) indan-5-ol, for obtaining **analgesia**, or as an adjunct to anaesthesia.
DERWENT CLASS: B03
INVENTOR(S): HAAPALINNA, A; LEHTIMAEKI, J; LEINO, T; VIITAMAA, T; VIRTANEN, R
PATENT ASSIGNEE(S): (ORIN) ORION CORP
COUNTRY COUNT: 94
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001000192	A2	20010104	(200111)*	EN	19
AU 2000055378	A	20010131	(200124)		

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001000192	A2	WO 2000-FI566	20000622
AU 2000055378	A	AU 2000-55378	20000622

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000055378	A Based on	WO 200100192

PRIORITY APPLN. INFO: US 1999-140795 19990625
AB WO 200100192 A UPAB: 20010224
NOVELTY - 3-(1-(1H-Imdazol-4-yl)-ethyl)-indan-5-ol (I), its esters or salts, can be administered intraspinally to obtain **analgesia** without side-effects, such as **sedation**, and can also be used as an adjunct to anaesthesia.
ACTIVITY - **Analgesic**.
MECHANISM OF ACTION - None given.
USE - For obtaining **analgesia**, e.g. treating intraoperative, postoperative, obstetric or chronic pain, and particularly for treating a spastic paraplegic; or as an adjunct to anaesthesia.
ADVANTAGE - Administration of (I) intrathecally at an **analgesic** dosage did not induce **sedation** in rats as **clonidine** did. Following intrathecal administration, results for the tail flick test were, for (I) ED50 0.3 mu g/rat, and for **clonidine** 6.4 mu g/rat; and results for decrease in spontaneous locomotor activity were, for (I) ED50 14 mu g/rat, and for **clonidine** 5 mu g/rat.
Dwg.0/1

L213 ANSWER 12 OF 83 MEDLINE
ACCESSION NUMBER: 68354556 MEDLINE
DOCUMENT NUMBER: 68354556 PubMed ID: 4233002
TITLE: [On the pharmacology of 2-(2,6-dimethylphenylamino)-4H-5,6-dihydro-1,3-thiazine (Bayer 1470), a substance inhibitory for adrenergic and cholinergic neurons].
Zur Pharmakologie von 2-(2,6-Dimethylphenylamino)-4H,5,6-

[redacted]

dihydro-1,3-thiazin (Bayer 1470), eines Hemmstoffes adrenergischer und cholinergischer Neurone.
AUTHOR: Kroneberg G; Oberdorf A; Hoffmeister F; Wirth W
SOURCE: NAUNYN-SCHMIEDEBERGS ARCHIV FUR EXPERIMENTELLE PATHOLOGIE UND PHARMAKOLOGIE, (1967) 256 (2) 257-80.
Journal code: BD8; 0054224.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 196809
ENTRY DATE: Entered STN: 19900101
Last Updated on STN: 20000303
Entered Medline: 19680916

L213 ANSWER 13 OF 83 MEDLINE
ACCESSION NUMBER: 69102977 MEDLINE
DOCUMENT NUMBER: 69102977 PubMed ID: 5707726
TITLE: [On the hypothermic effect of some pharmacological agents]. O gipotermicheskom deistvii nekotorykh farmakologicheskikh sredstv.
AUTHOR: Uriupov O Iu
SOURCE: FARMAKOLOGIIA I TOKSIKOLOGIIA, (1968 Sep-Oct) 31 (5) 568-71.
Journal code: ETR; 16920420R. ISSN: 0014-8318.
PUB. COUNTRY: USSR
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 196903
ENTRY DATE: Entered STN: 19900101
Last Updated on STN: 19980206
Entered Medline: 19690319

L213 ANSWER 14 OF 83 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 75125291 EMBASE
DOCUMENT NUMBER: 1975125291
TITLE: Anesthetic management of patients with cardiac diseases (Japanese).
AUTHOR: Okazaki K.
CORPORATE SOURCE: Dept. Anesthes., Univ. Hosp., Tokushima, Japan
SOURCE: Japanese Journal of Anesthesiology, (1974) 23/9 (787-796).
CODEN: MASUAC
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
024 Anesthesiology
LANGUAGE: Japanese
AB From experimental measurements of myocardial contractility in dogs, using clinical doses of halothane, methoxyflurane, thalamonal, ketamine and diethyl ether respectively, it was shown that the depressive effects of 1% halothane or methoxyflurane on V max were marked. The need for exact and continuous circulatory monitoring with non invasive methods during anesthesia is emphasized. (21 references.)

L213 ANSWER 15 OF 83 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 79012218 EMBASE
DOCUMENT NUMBER: 1979012218
TITLE: Pharmacological studies on 3-[.gamma.-(p-fluorobenzoyl)propyl]-2,3,4,4a,5,6-hexahydro-1-(H)-pyrazino(1,2-a)quinoline hydrochloride (compound 69/183). Part IV: Other CNS effects and acute toxicity.
AUTHOR: Singh G.B.; Srimal R.C.; Dhawan B.N.
CORPORATE SOURCE: Cent. Drug Res. Inst., Lucknow, India

SOURCE: Arzneimittel-Forschung/Drug Research, (1978) 28/9 (1641-1644).
CODEN: ARZNAD
COUNTRY: Germany
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: German

L213 ANSWER 16 OF 83 MEDLINE
ACCESSION NUMBER: 80113098 MEDLINE
DOCUMENT NUMBER: 80113098 PubMed ID: 6101554
TITLE: Noradrenergic and serotonergic mediation of spinal analgesia mechanisms.
AUTHOR: Zemlan F P; Corrigan S A; Pfaff D W
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1980 Jan 25) 61 (2) 111-24.
Journal code: EN6; 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198004
ENTRY DATE: Entered STN: 19900315
Last Updated on STN: 19950206
Entered Medline: 19800423

L213 ANSWER 17 OF 83 MEDLINE
ACCESSION NUMBER: 82114049 MEDLINE
DOCUMENT NUMBER: 82114049 PubMed ID: 7326417
TITLE: [Analgesic effect of clopheline].
K voprosu ob anal'geticheskom effekte klofelina.
AUTHOR: Zaitsev A A; Ignatov Iu D; Dmitriev A V
SOURCE: BIULLETEN EKSPERIMENTALNOI BIOLOGII I MEDITSINY, (1981 Dec) 92 (12) 690-2.
Journal code: A74; 0370627. ISSN: 0365-9615.
PUB. COUNTRY: USSR
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198204
ENTRY DATE: Entered STN: 19900317
Last Updated on STN: 19900317
Entered Medline: 19820412

AB Clophelin significantly decreases the intensity of behavioral and hemodynamic manifestations of nociceptive reactions and inhibits spontaneous behavior only in doses exerting a powerful hypotensive action in normotensive unrestrained cats (0.02-0.03 mg/kg) and rats (2-4 mg/kg). A similar correlation between the inhibition of nociceptive reactions and hypotension was revealed in experiments with papaverine (5-8 mg/kg). Naloxone averts the clopheline-induced hypotension and inhibition of the emotional and behavioral manifestations rather than recovers the hemodynamic nociceptive reactions. It is assumed that clophelin has no genuine morphine-like analgetic action.

L213 ANSWER 18 OF 83 MEDLINE
ACCESSION NUMBER: 81205182 MEDLINE
DOCUMENT NUMBER: 81205182 PubMed ID: 6112935
TITLE: Studies in the primate on the analgetic effects associated with intrathecal actions of opiates, alpha-adrenergic agonists and baclofen.
AUTHOR: Yaksh T L; Reddy S V
CONTRACT NUMBER: NIDA 02110 (NIDA)

[redacted]

SOURCE: ANESTHESIOLOGY, (1981 Jun) 54 (6) 451-67.
Journal code: 4SG; 1300217. ISSN: 0003-3022.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198107
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19950206
Entered Medline: 19810723

AB The effects of intrathecally administered opiates (morphine sulfate and meperidine), alpha-adrenergic agonists (clonidine and ST-91) and baclofen were examined on the shock titration threshold of macaque monkeys chronically prepared with intrathecal (I) or epidural (E) catheters. Spinal opiates produced a long-lasting analgesia which was antagonized by naloxone. The order of potency was I morphine greater than I meperidine greater than E meperidine greater than E morphine. Clonidine and ST-91, also produced a dose-dependent, long-lasting elevation in the shock titration threshold, antagonized by phentolamine, but not naloxone. L-baclofen, but not D-baclofen, resulted in a dose-dependent elevation of shock titration threshold, which was not antagonized by naloxone. Repeated administration at 24-h intervals over a 7-day period of morphine, clonidine or baclofen, resulted in a significant reduction in the analgetic effects of each drug. Cross tolerance between the three classes of agents was not observed. Intrathecal co-administration of inactive doses of ST-91 and morphine resulted in a near maximal increase in the shock titration threshold, which failed to show any significant tolerance over 21 days. Intrathecal ST-91 and morphine produced no change in either muscle strength, tendon reflexes, respiratory rate, urine formation, or the ability to locomote. Baclofen, in contrast, produced a dose-dependent decrease in muscle strength. That the intrathecal drugs did not produce anesthesia was demonstrated by their failure to block the avoidance response to ensuing ear shock cued by a light tactile stimulus applied to the hind paw. These results clearly indicate that a powerful analgesia can be produced by selectively activating adrenergic, opiate, and baclofenergic receptor systems in the spinal cord.

L213 ANSWER 19 OF 83 MEDLINE
ACCESSION NUMBER: 81164728 MEDLINE
DOCUMENT NUMBER: 81164728 PubMed ID: 6111465
TITLE: Characterization of alpha-adrenoceptors participating in the central hypotensive and sedative effects of clonidine using yohimbine, rauwolscine and corynanthine.
AUTHOR: Timmermans P B; Schoop A M; Kwa H Y; Van Zwieten P A
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1981 Mar 5) 70 (1) 7-15.
Journal code: EN6; 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198106
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19950206
Entered Medline: 19810623

AB The central alpha-adrenoceptors responsible for mediating the clonidine-induced central hypotension in anaesthetized cats and sedation in mice have been characterized according to their sensitivities to the alpha-adrenoceptor antagonist yohimbine and its two diastereomeric congeners rauwolscine and corynanthine. Yohimbine and rauwolscine (1-10 microgram/kg) dose-dependently antagonized the central hypotensive response to clonidine (1 microgram/kg) applied 15 min later. Greater amounts of corynanthine (30-100 micrograms/kg) had to be administered to diminish the central depressor effect of clonidine. In these studies the

drugs were infused via the left vertebral artery. The prolongation of the hexobarbitone-induced loss of the righting reflex in mice by clonidine (0.3 mg/kg, i.p.) was inhibited by previous treatment with yohimbine and rauwolscine (0.04-5 mg/kg, i.p.) in a dose-dependent manner, but not by corynanthine. Binding experiments with rat isolated cerebral membranes demonstrated the higher affinity of yohimbine and rauwolscine for the [3H] clonidine- than for the [3H]prazosin-specific binding sites. The reverse was found for corynanthine. The relative potencies of yohimbine, rauwolscine and corynanthine in inhibiting these central effects of clonidine are comparable to their order of efficacies in blocking peripheral alpha 2-adrenoceptors. Accordingly, clonidine-induced central hypotension and sedation are mediated by alpha 2-adrenoceptors.

L213 ANSWER 20 OF 83 MEDLINE
ACCESSION NUMBER: 83091735 MEDLINE
DOCUMENT NUMBER: 83091735 PubMed ID: 6817371
TITLE: Chlorpromazine hyperalgesia antagonizes clonidine analgesia, but enhances morphine analgesia in rats tested in a hot-water tail-flick paradigm.
AUTHOR: Gleeson R M; Atrens D M
SOURCE: PSYCHOPHARMACOLOGY, (1982) 78 (2) 141-6.
Journal code: QGI; 7608025. ISSN: 0033-3158.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198302
ENTRY DATE: Entered STN: 19900317
Last Updated on STN: 19900317
Entered Medline: 19830214

AB Seventy-six male Sprague-Dawley rats were tested in a hot-water (55 degrees +/- 0.5 degrees C) tail-flick paradigm. Tail-flick latencies (TFL) were obtained at 30 and 15 min before intraperitoneal injection of either morphine (2.5, 5.0 and 10.0 mg/kg) clonidine (25, 50, 100 and 200 microgram/kg), chlorpromazine (CPZ, 2.5 and 5.0 mg/kg), dual injections of these drug combinations, or a saline control injection. Further TFL measures were taken immediately following drug administration and thereafter at 15 min intervals. The mean of the pre-drug TFL's served as each rat's baseline. All other TFL's were calculated as percentage changes from that baseline. Mean changes were determined for each treatment group and differences between groups, at each test time, were analysed. Our results demonstrated morphine and clonidine analgesia but CPZ hyperalgesia. The drug interaction studies revealed that morphine analgesia is enhanced by co-administration of either clinidine or CPZ but that clonidine analgesia is antagonized by chlorpromazine. These data suggest that morphine and clonidine exert their analgesic effects through different neurochemical mechanisms. It is particularly interesting that the clonidine-CPZ combination should result in TFL's similar to baseline levels, even though both drugs are sedatives. The investigation emphasizes the value of chlorpromazine as a pharmacological tool in analgesic research because of its ability to induce hyperalgesia even though it is a sedating agent.

L213 ANSWER 21 OF 83 MEDLINE
ACCESSION NUMBER: 83061662 MEDLINE
DOCUMENT NUMBER: 83061662 PubMed ID: 6128647
TITLE: Antinociceptive activity of clonidine in the mouse, rat and dog.
AUTHOR: Skingle M; Hayes A G; Tyers M B
SOURCE: LIFE SCIENCES, (1982 Sep 13) 31 (11) 1123-32.
Journal code: L62; 0375521. ISSN: 0024-3205.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

[redacted]

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198301
ENTRY DATE: Entered STN: 19900317
Last Updated on STN: 19950206
Entered Medline: 19830119

AB The antinociceptive activities of clonidine have been determined against several qualitatively different noxious stimuli in the mouse, rat and dog. In these tests clonidine given subcutaneously was 6 to 7 times more potent than morphine. Both clonidine and morphine were more potent against responses to heat induced nociceptive stimuli than against responses to heat induced nociception or that induced by electrical tail stimulation. However, unlike morphine the effects of clonidine in these latter tests were only seen at doses that also caused sedation and so these animals were less able to respond to the nociceptive stimuli. In contrast in pressure, chemical and tooth pulp stimulation tests clonidine produced increases in nociceptive thresholds at doses which caused no overt signs of behavioural depression. Comparisons of the relative potencies of clonidine and the less lipophilic analogue 4-hydroxyclonidine given subcutaneously and intracerebroventricularly indicate that clonidine induced antinociception is predominantly centrally mediated. However, a peripheral component may also be present in the inhibition of acetylcholine-induced abdominal constriction in the mouse.

L213 ANSWER 22 OF 83 MEDLINE
ACCESSION NUMBER: 84232861 MEDLINE
DOCUMENT NUMBER: 84232861 PubMed ID: 6733365
TITLE: Selective antinociceptive effects of tizanidine (DS 103-282), a centrally acting muscle relaxant, on dorsal horn neurones in the feline spinal cord.
AUTHOR: Davies J; Johnston S E
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (1984 Jun) 82 (2) 409-21. Journal code: B00; 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198408
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19840813

AB The effects of the centrally acting muscle relaxant tizanidine (DS 103-282) have been examined on the responses of laminae IV and V dorsal horn neurones to peripheral noxious and non-noxious stimuli in cats spinalized at L1. Iontophoretic ejection of tizanidine near the cell bodies of the recorded neurones or more dorsally into laminae II-III resulted in a marked and prolonged depression of excitation of laminae IV and V neurones evoked by noxious stimuli. Spontaneous firing was also depressed in many neurons but responses to innocuous stimuli were unaffected. Intravenous administration of tizanidine also produced a long lasting and selective reduction in responses of laminae IV and V neurones to noxious stimuli and depressed the long latency excitation of these neurones evoked by electrical stimulation of small diameter unmyelinated primary afferents. In contrast to the selective antinociceptive effect of tizanidine, ejection of gamma-aminobutyric acid (GABA) near laminae IV and V neurones or isoguvacine into laminae II-III produced parallel reductions in responses to noxious and non-noxious stimuli. Furthermore, ejections of the excitant amino acid kainate into laminae II-III produced parallel enhancement of responses induced by both types of stimuli. The site and mechanism of the antinociceptive action of tizanidine is not known but does not appear to involve an interaction with opiate receptors as it was not antagonized by naloxone. The possibility is discussed that tizanidine acts at synapses formed between excitatory interneurones in lamina II or

III and laminae IV and V neurones, either interfering with transmitter release or its postsynaptic action. The effects of iontophoretically administered tizanidine are quite distinct from those of baclofen, which produced non-selective depression of responses to both noxious and innocuous stimuli, but were similar to those of noradrenaline. This raises the possibility that noradrenaline and tizanidine may act at a common site in the spinal cord.

L213 ANSWER 23 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:572042 CAPLUS
DOCUMENT NUMBER: 103:172042
TITLE: Action of drugs and chemical agents on rat liver regeneration
AUTHOR(S): Gershbein, Leon L.; Pedroso, Aldo F.
CORPORATE SOURCE: Northwest Inst. Med. Res., Chicago, IL, 60634, USA
SOURCE: Drug Chem. Toxicol. (1977) (1985), 8(3), 125-43
CODEN: DCTODJ; ISSN: 0148-0545
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A large no. (> 270) of drugs, chems., and other agents were tested for their effects on the regeneration of liver in hepatectomized rats. Seven anticonvulsants, 4 antiinflammatory drugs, 4 sedatives-hypnotics, the antipyretic-analgesic aminopyrine [58-15-1], the antifungal griseofulvin [126-07-8], a uricosuric, a muscle relaxant, a hydrocholeretic, an antihypertensive, and a thyroid inhibitor were hepatotrophic. Most the remaining drugs were inactive in this screening, whereas a few suppressed liver regeneration.
IT **55-65-2 4205-90-7 40580-59-4**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(liver regeneration response to)

L213 ANSWER 24 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:553223 CAPLUS
DOCUMENT NUMBER: 103:153223
TITLE: In vitro inhibition studies of two isozymes of human liver cytochrome P-450. Mephenytoin p-hydroxylase and sparteine monooxygenase
AUTHOR(S): Inaba, Tadanobu; Jurima, Malle; Mahon, William A.; Kalow, Werner
CORPORATE SOURCE: Dep. Pharmacol., Univ. Toronto, Toronto, ON, M5S 1A8, Can.
SOURCE: Drug Metab. Dispos. (1985), 13(4), 443-8
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Human liver prepns. were used to screen various drugs for their capability of binding to mephenytoin p-hydroxylase [96779-46-3] and sparteine monooxygenase [90119-12-3], 2 cytochrome P 450 [9035-51-2]-catalyzed activities that are independently heritable. For this screening, any indication of competitive inhibition by the drug was interpreted as an indication of binding. Among 64 drugs and alkaloids tested, 24 compds. caused inhibition of mephenytoin p-hydroxylation but the inhibition was weak in most cases; by contrast, 40 of the 64 compds. inhibited sparteine oxidn., the inhibition being potent in many cases. The only fairly strong inhibitors of mephenytoin p-hydroxylation were the alkaloid papaverine and MAO inhibitors tranylcypromine and nialamide. The results of these inhibition studies confirm the independence of the 2 monogenic defects obsd. in different populations. Metab. is possibly altered in poor metabolizers of mephenytoin with fewer drugs than in poor metabolizers of sparteine.
IT **4205-90-7**
RL: BIOL (Biological study)

(cytochrome P 450 isozymes of human liver response to, phenotypes in relation to)

L213 ANSWER 25 OF 83 MEDLINE
ACCESSION NUMBER: 86147240 MEDLINE
DOCUMENT NUMBER: 86147240 PubMed ID: 4094657
TITLE: The analgesic activity of a clonidine analog. The formamidine, U-47,476A.
AUTHOR: Mohrland J S; Von Voigtlander P F
SOURCE: NEUROPHARMACOLOGY, (1985 Dec) 24 (12) 1207-10.
Journal code: NZB; 0236217. ISSN: 0028-3908.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198604
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860407

AB A compound structurally related to clonidine, N,N-dimethyl-N'-(2,4, 6-trimethyl phenyl)formamidine hydrochloride (U-47,476A), was evaluated for analgesic activity; it produced a significant analgesia in mice and rats in several analgesiometric procedures. The analgesic potency varied considerably with different analgesiometric tests, with ED50s ranging from 0.4 mg/kg for writhing in mice induced by hydrochloric acid to greater than 30 mg/kg for the tail-flick test in rats. Although the potency was less than that of clonidine, it was still in the range of pentazocine. Then U-47,476A was further examined to determine whether the analgesic effect was mediated by alpha-adrenergic mechanisms and accompanied by hypotension and sedation, similar to that produced by clonidine. The drug U-47,476A failed to lower significantly blood pressure in rats given 10 and 30 mg/kg subcutaneously, suggesting a possible separation of the hypotensive and analgesic properties of this compound. The locomotor activity of mice was unaltered after 0.5 mg/kg of U-47,476A; however, a significant decrease in activity was observed after the administration of 5 mg/kg. The effect of U-47,476A on locomotor activity in the mouse was significantly less than that for an approximately equipotent analgesic dose of clonidine. The analgesic effect of U-47,476A was antagonized by yohimbine, but not by reserpine, naloxone or phentolamine, Thus, the attenuation of the response to noxious stimuli by U-47,476A is mediated by alpha 2-adrenoceptors and not by opioid receptors or presynaptic monoaminergic mechanisms, similar to clonidine-induced analgesia.

L213 ANSWER 26 OF 83 MEDLINE
ACCESSION NUMBER: 86063469 MEDLINE
DOCUMENT NUMBER: 86063469 PubMed ID: 4068389
TITLE: Diversity of underlying mechanisms in the production of analgesic and pentobarbital-hypnosis prolonging effects of various analgesic drugs and stresses.
AUTHOR: Hanada S; Deguchi Y; Kaneto H
SOURCE: JAPANESE JOURNAL OF PHARMACOLOGY, (1985 Sep) 39 (1) 117-9.
Journal code: KO7; 2983305R. ISSN: 0021-5198.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198601
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860115

AB Stressful stimuli, electric footshock (FS), immobilized-water immersion (IW), and cold-water swimming (CWS), produced analgesia and prolonged the pentobarbital hypnosis as well as morphine and clonidine. Naloxone

completely antagonized the analgesic effects of morphine and FS and partially that of IW; however, that of clonidine and CWS were not reversed by naloxone. Naloxone eliminated the hypnosis prolonging effect of morphine and FS, but failed to reverse the effect of clonidine, IW and CWS. Differences in the analgesic and hypnosis prolonging effects and also the respective naloxone sensitivity of each drug and stress suggest the diversity of the underlying mechanisms.

L213 ANSWER 27 OF 83 MEDLINE
ACCESSION NUMBER: 85225315 MEDLINE
DOCUMENT NUMBER: 85225315 PubMed ID: 4004750
TITLE: [Clonidine as a sedative in horses].
Clonidin als Sedativum beim Pferd.
AUTHOR: Wintzer H J; Krause D; Siedentopf C; Frey H H
SOURCE: BERLINER UND MUNCHENER TIERARZTLICHE WOCHENSCHRIFT, (1985 May 1) 98 (5) 190-3.
Journal code: 9Q8; 0003163. ISSN: 0005-9366.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198507
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19850724

L213 ANSWER 28 OF 83 MEDLINE
ACCESSION NUMBER: 85185638 MEDLINE
DOCUMENT NUMBER: 85185638 PubMed ID: 2859378
TITLE: Pharmacological evidence for the involvement of alpha-2 adrenoceptors in the sedative effect of detomidine, a novel sedative-analgesic.
AUTHOR: Virtanen R; Ruskoaho H; Nyman L
SOURCE: JOURNAL OF VETERINARY PHARMACOLOGY AND THERAPEUTICS, (1985 Mar) 8 (1) 30-7.
Journal code: KCP; 7910920. ISSN: 0140-7783.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198506
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19950206
Entered Medline: 19850614

AB The sedative effect and mechanism of action of a novel imidazole derivative, detomidine, were studied in laboratory animals. Three methods were used to quantify drug-induced sedation: (i) decrease in spontaneous activity of mice; (ii) increase in barbiturate induced anaesthesia time in mice; (iii) loss of righting reflex in chicks. Clonidine and xylazine were included in the studies for comparison. The sedative potency of detomidine was shown to be approximately equal to that of clonidine and much higher than that of xylazine. In all tests, the sedative effect of detomidine was inhibited by antagonists of alpha-2 adrenoceptors (yohimbine, rauwolscine and idazoxan) but not by alpha-1 antagonists (prazosin, corynanthine). Furthermore, an ex vivo receptor binding study in the rat showed that detomidine-induced decrease in spontaneous activity was significantly correlated to [3H]clonidine but not to [3H]prazosin displacement in brain membranes. These results show that detomidine has potent sedative effects in mice, rats and chicks, and suggest that this action is mediated through stimulation of alpha-2 adrenoceptors.

L213 ANSWER 29 OF 83 MEDLINE
ACCESSION NUMBER: 85154300 MEDLINE

[redacted]

DOCUMENT NUMBER: 85154300 PubMed ID: 2984021
TITLE: Evaluation of the alpha 1- and alpha 2-adrenoceptor effects of detomidine, a novel veterinary sedative analgesic.
AUTHOR: Virtanen R; Nyman L
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1985 Jan 22) 108 (2) 163-9.
Journal code: EN6; 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198505
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19970203
Entered Medline: 19850515

AB The in vitro receptor interactions of detomidine, a novel veterinary sedative analgesic, were studied. Detomidine caused a concentration-dependent inhibition of the twitch response in electrically stimulated mouse vas deferens with a pD2 value of 8.8. Clonidine and xylazine had the same effect with pD2 values of 8.7 and 7.5, respectively. The effect of detomidine was competitively antagonized by the alpha 2-blocking agents yohimbine, rauwolscine and idazoxan but not by the alpha 1-antagonists prazosin and corynanthine. The effect of detomidine was not antagonized by the opioidergic antagonist naloxone, the dopaminergic antagonist sulpiride, the serotonergic antagonist methysergide, the histamine H2-antagonist cimetidine, the histamine H1-antagonist diphenhydramine and the cholinergic muscarine antagonist atropine. Detomidine, as well as clonidine and xylazine, produced concentration-dependent contractions of rat anococcygeal muscle and rabbit aortic strips with pD2 values between 2.5 and 6.4. Intrinsic activities (compared to phenylephrine) varied between 0.5 and 0.7. The effects of detomidine in these two muscles could be antagonized by low concentrations of prazosin. In receptor binding experiments detomidine showed strong affinity to alpha 2-receptors. There was some binding affinity towards alpha 1-receptors also but only negligible or no affinity towards dopamine, opiate and adenosine receptors. In conclusion, the present results suggest that detomidine is a potent alpha 2-adrenoceptor agonist and that at high concentrations it can also stimulate alpha 1-adrenoceptors.

L213 ANSWER 30 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1987:43448 CAPLUS
DOCUMENT NUMBER: 106:43448
TITLE: CASE study of in vitro inhibition of sparteine monooxygenase
AUTHOR(S): Klopman, Gilles; Venegas, Ruben E.
CORPORATE SOURCE: Dep. Chem., Case West. Reserve Univ., Cleveland, OH, 44106, USA
SOURCE: Acta Pharm. Jugosl. (1986), 36(2), 189-209
CODEN: APJUA8; ISSN: 0001-6667
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The Computer Automated Structure Evaluation program (CASE) has been used to analyze the in vitro inhibition of sparteine monooxygenase [90119-12-3]. A significant correlation between the Log10 P (1-octanol/water) of the 74 drugs studied and their inhibitory potency is obsd.

IT **55-65-2**, Guanethidine **2165-19-7**, Guanoxan **4205-90-7**, Clonidine
RL: BIOL (Biological study)
(sparteine monooxygenase inhibition by, computer automated structure evaluation of)

L213 ANSWER 31 OF 83 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1986:400533 CAPLUS
DOCUMENT NUMBER: 105:533
TITLE: Alpha-adrenoceptor-mediated antinociception and sedation in the rat and dog
AUTHOR(S): Hayes, A. G.; Skingle, M.; Tyers, M. B.
CORPORATE SOURCE: Dep. Neuropharmacol., Glaxo Group Res. Ltd., Ware/Herts., SG12 0DJ, UK
SOURCE: Neuropharmacology (1986), 25(4), 391-6
CODEN: NEPHBW; ISSN: 0028-3908
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The potency of a range of .alpha.-adrenoceptor agonists in producing antinociception and sedation in the rat and dog was compared. In the rat, the selective .alpha.2-adrenoceptor agonists, guanabenz acetate [**23256-50-0**], UK 14304 tartrate [59803-99-5] and guanfacine [**29110-47-2**], were more potent as sedative agents than as antinociceptive agents. For compds. which have similar activities at both .alpha.1- and .alpha.2-adrenoceptors, such as clonidine [**4205-90-7**], alinidine [33178-86-8], oxymetazoline [1491-59-4] and naphazoline [835-31-4], there was little sepn. between EDs for antinociception and sedation. In marked contrast, the selective .alpha.1-adrenoceptor agonists, ST 587 [15327-38-5] and methoxamine [390-28-3], were more potent as antinociceptive agents than as sedatives. Similarly, ICI 106270 [67249-51-8] and CP 18534-1 [76280-95-0], 2 agonists with a greater .alpha.1-/.alpha.2-adrenoceptor ratio than clonidine, were also more potent in antinociceptive tests than in sedative tests. In the conscious dog, clonidine was 8-10 times more potent than ICI 106270 and CP 18534 at increasing nociceptive thresholds to mild elec. stimulation of the toothpulp. At equiantinociceptive doses, the ranked order of potency for inducing sedation was clonidine .gtoreq. ICI 106270 > CP 18534-1. Dose-related bradycardia was also induced by each of the 3 .alpha.-adrenoceptor agonists at antinociceptive doses. Apparently antinociceptive activity can probably be mediated by either .alpha.1- or .alpha.2-adrenoceptors, whereas sedation appears to be mediated solely by the .alpha.2-subtype. Thus, it may be possible to sep. the antinociceptive and sedative effects of sympathomimetic agents, but it is unlikely that these agents would be completely devoid of cardiovascular effects.

IT **4205-90-7 23256-50-0 29110-47-2**
RL: BIOL (Biological study)
(analgesic and sedative activity of, .alpha.-adrenergic receptors mediation of)

L213 ANSWER 32 OF 83 MEDLINE
ACCESSION NUMBER: 87182446 MEDLINE
DOCUMENT NUMBER: 87182446 PubMed ID: 3565815
TITLE: Epidural clonidine produces antinociception, but not hypotension, in sheep.
AUTHOR: Eisenach J C; Dewan D M; Rose J C; Angelo J M
CONTRACT NUMBER: GM35523 (NIGMS)
SOURCE: ANESTHESIOLOGY, (1987 Apr) 66 (4) 496-501.
Journal code: 4SG; 1300217. ISSN: 0003-3022.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198704
ENTRY DATE: Entered STN: 19900303
Last Updated on STN: 19970203
Entered Medline: 19870430

AB Intrathecally administered clonidine produces analgesia, but also produces hypotension. To assess the effects of epidural administration, the authors inserted lumbar epidural catheters in seven nonpregnant ewes, and

injected, on separate days, clonidine (50-750 mcg), morphine (5-10 mg), and a clonidine-morphine combination (clonidine 150 mcg + morphine 5 mg). Clonidine produced dose-dependent antinociception and sedation, with the lowest maximally effective antinociceptive dose being 300 mcg. Morphine produced less intense antinociception than clonidine, and did not potentiate clonidine's effect. Antinociception, but not sedation, following clonidine injection was reversed by epidural injection of the alpha 2-adrenergic antagonist, idazoxan. Epidurally administered naloxone and prazosin did not reverse clonidine's antinociceptive effect, nor did intravenously administered idazoxan. Epidurally administered clonidine did not decrease blood pressure or heart rate or affect arterial blood gas tensions or spinal cord histology. These data suggest that epidurally administered clonidine produces analgesia by a local, alpha 2-adrenergic mechanism. In sheep, epidurally administered clonidine does not produce hypotension.

L213 ANSWER 33 OF 83 MEDLINE
ACCESSION NUMBER: 88175441 MEDLINE
DOCUMENT NUMBER: 88175441 PubMed ID: 2895432
TITLE: Analgesic effects of intrathecally-applied alpha 2-adrenoceptor agonists in conscious, unrestrained sheep.
AUTHOR: Waterman A; Livingston A; Bouchenafa O
CORPORATE SOURCE: Dept. Veterinary Surgery, University of Bristol.
SOURCE: NEUROPHARMACOLOGY, (1988 Feb) 27 (2) 213-6.
Journal code: NZB; 0236217. ISSN: 0028-3908.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198805
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19880506

AB Intrathecal injections of small volumes of the alpha 2-adrenoceptor agonists, xylazine and clonidine, into the cervical region of the spinal cord of conscious unrestrained sheep produced a dose-dependent analgesia of the forelimbs as measured using a mechanical pressure device. Intravenous injection of the alpha 2-adrenoceptor antagonist, idazoxan completely abolished the analgesic effects of the intrathecally applied alpha 2-adrenoceptor agonists. Subsequent studies using [3H] clonidine injected at a similar dose and volume via the intrathecal catheters, indicated that the volume of drug used, 100 microliter, gave a localisation of the drug limited to about five vertebral segments around the catheter tip.

L213 ANSWER 34 OF 83 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1989:587359 CAPLUS
DOCUMENT NUMBER: 111:187359
TITLE: A comparison of the analgesic effects of intrathecal .alpha.2 adrenoceptor agonists and opioids in conscious unrestrained sheep
AUTHOR(S): Ley, S.; Dash, A.; Waterman, A.; Livingston, A.
CORPORATE SOURCE: Dep. Pharmacol., Univ. Bristol, Bristol, BS8 1TD, UK
SOURCE: Adv. Biosci. (Oxford) (1989), 75(Prog. Opioid Res.), 495-8
CODEN: AVBIB9; ISSN: 0065-3446
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Intrathecal catheters were implanted into the spinal canals of adult sheep to terminate at the level of either cervical vertebra 4 or lumbar vertebra 5, and threshold mech. pressure pain tests were made on the fore or hind limbs, resp. The antinociceptive effects of the .alpha.2-adrenoceptor agonists xylazine and clonidine and of the opioids morphine, fentanyl, and

U50488H, given in vols. of 100 .mu.L, were measured. Low doses of xylazine (5-50 .mu.g) and clonidine (3-35 .mu.g) produced a dose-dependent antinociceptive action which was abolished by the .alpha.2-adrenoceptor antagonist idazoxan (100 .mu.g/kg, i.v.). U50488H (350-2000 .mu.g) and fentanyl (5-100 .mu.g) produced almost no antinociceptive effects, while morphine (500-3000 .mu.g) had only a slight antinociceptive effect. Thus, in the conscious unrestrained sheep the intrathecally applied opioids of both the .mu.- and .kappa.-types are far less effective at raising nociceptive thresholds to mech. pressure than the .alpha.2-adrenoceptor agonists.

IT **4205-90-7**, Clonidine
RL: BIOL (Biological study)
(analgesia from, after intrathecal administration, in **sheep**)

L213 ANSWER 35 OF 83 MEDLINE
ACCESSION NUMBER: 90137176 MEDLINE
DOCUMENT NUMBER: 90137176 PubMed ID: 2615916
TITLE: Effects of tizanidine, eperisone and afloqualone on feline dorsal horn neuronal responses to peripheral cutaneous noxious and innocuous stimuli.
AUTHOR: Davies J
CORPORATE SOURCE: Department of Pharmacology, School of Pharmacy, London, U.K.
SOURCE: NEUROPHARMACOLOGY, (1989 Dec) 28 (12) 1357-62.
Journal code: NZB; 0236217. ISSN: 0028-3908.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199003
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19960129
Entered Medline: 19900306

AB The effects of eperisone and afloqualone have been compared with those of tizanidine on excitatory responses of spinal dorsal horn neurones, evoked by noxious and innocuous peripheral stimuli. Tizanidine, administered intravenously or iontophoretically, resulted in a profound, long-lasting and selective depression of the responses to noxious stimuli. In contrast, intravenous injection of eperisone produced either a rapidly reversible depression of responses to both noxious and innocuous stimuli or had no effect on these responses. Iontophoretic administration of eperisone also reduced neuronal responses to both forms of peripheral stimuli and that induced by quisqualate. This depressant action of eperisone was rapidly reversible but was often accompanied by a reduction of the amplitude of the action potentials. Afloqualone had no depressant action on any evoked response when administered iontophoretically. However, intravenous injection of this agent resulted in weak depressant effects on responses to noxious, innocuous or both types of stimuli, of a few of the neurones tested. This effect of afloqualone was not dose-dependent and was mimicked by control injections of the vehicle in which it was suspended. It is suggested that the muscle relaxants, eperisone and afloqualone, in contrast to tizanidine, do not possess any direct spinal antinociceptive activity.

L213 ANSWER 36 OF 83 MEDLINE
ACCESSION NUMBER: 90046409 MEDLINE
DOCUMENT NUMBER: 90046409 PubMed ID: 2573052
TITLE: Adaptive changes in alpha-2 adrenoceptor mediated responses: analgesia, hypothermia and hypoactivity.
AUTHOR: Minor B G; Danysz W; Jonsson G; Mohammed A K; Post C; Archer T
CORPORATE SOURCE: Astra Pain Control and Research Centre, Sodertalje, Sweden.
SOURCE: PHARMACOLOGY AND TOXICOLOGY, (1989 Aug) 65 (2) 143-51.

[redacted]

Journal code: PHT; 8702180. ISSN: 0901-9928.
PUB. COUNTRY: Denmark
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198912
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19950206
Entered Medline: 19891205

AB The acute effects of the alpha-2 adrenoceptor agonists, clonidine and guanfacine, upon antinociception, hypothermia and motor activity were compared under conditions of receptor antagonism, denervation, and chronic administration of a tricyclic antidepressant compound. The analgesic actions of clonidine and guanfacine were antagonised by idazoxan, an alpha-2 receptor antagonist, but potentiated by pretreatment with the noradrenaline neurotoxin DSP4, and attenuated by chronic treatment with desipramine (DMI). Clonidine- and guanfacine-induced hypothermia was antagonised by idazoxan, potentiated by prior treatment with DSP4 and attenuated by chronic administration with DMI. Both clonidine and guanfacine produced decreases in motor activity that were attenuated by idazoxan but unaffected by prior DSP-4 treatment. Chronic DMI administration also attenuated clonidine-induced hypoactivity but potentiated guanfacine-induced hypoactivity. These diverse results describe both similar and differential adaptive mechanisms modulating the functional effect of alpha-2 receptor systems in the central nervous system.

L213 ANSWER 37 OF 83 MEDLINE
ACCESSION NUMBER: 89349701 MEDLINE
DOCUMENT NUMBER: 89349701 PubMed ID: 2548415
TITLE: Intrathecal clonidine suppresses noxiously evoked activity of spinal wide dynamic range neurons in cats.
AUTHOR: Murata K; Nakagawa I; Kumeta Y; Kitahata L M; Collins J G
CORPORATE SOURCE: Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut 06510.
CONTRACT NUMBER: NS-09871 (NINDS)
SOURCE: ANESTHESIA AND ANALGESIA, (1989 Aug) 69 (2) 185-91.
Journal code: 4R8; 1310650. ISSN: 0003-2999.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198909
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19970203
Entered Medline: 19890912

AB The analgesic effectiveness of perispinal clonidine administration prompted us to evaluate clonidine effects on spinal dorsal horn wide dynamic range neurons. Intrathecal clonidine produced a dose-dependent (10 and 30 micrograms), yohimbine-reversible suppression of noxiously evoked activity in decerebrate, spinal cord-transected cats. In addition, combining ineffective intrathecal doses of morphine (25 micrograms) and clonidine (5 micrograms) produced statistically significant, reversible suppression of noxiously evoked activity. The time course of suppression was similar to that observed behaviorally. These results support the role of spinal alpha 2-adrenergic receptors in clonidine analgesia.

L213 ANSWER 38 OF 83 MEDLINE
ACCESSION NUMBER: 89103954 MEDLINE
DOCUMENT NUMBER: 89103954 PubMed ID: 2912316
TITLE: Epidural clonidine analgesia in obstetrics: sheep studies.
AUTHOR: Eisenach J C; Castro M I; Dewan D M; Rose J C
CORPORATE SOURCE: Department of Anesthesia, Wake Forest University, Bowman

Gray School of Medicine, Winston-Salem, North Carolina 27103.
CONTRACT NUMBER: FD-R-000171 (FDA)
GM35523 (NIGMS)
SOURCE: ANESTHESIOLOGY, (1989 Jan) 70 (1) 51-6.
Journal code: 4SG; 1300217. ISSN: 0003-3022.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198902
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19890213

AB Epidural clonidine administration produces analgesia by a nonopiate, spinal mechanism, and offers advantages over other epidural agents for labor analgesia. To examine clonidine's acute maternal and fetal effects, the authors injected clonidine, 300 micrograms, epidurally in seven chronically prepared, near term ewes. Unlike epidural saline injection, clonidine increased maternal and fetal serum glucose (by 178 +/- 30% and 190 +/- 30%, respectively; mean +/- SEM, P less than .01) 1 h following injection. Maternal and fetal serum cortisol and arterial blood gas tensions were unchanged following clonidine. Epidural clonidine injection produced minor decreases (10-15%) in heart rate in ewe and fetus, without altering maternal and fetal blood pressure, intra-uterine pressure, or uterine blood flow. Maternal and fetal serum clonidine concentrations peaked at 58 +/- 8 and 73 +/- 5 min following injection, respectively, and declined with similar half-lives. Heart rate correlated negatively with serum clonidine concentration in both ewe and fetus (P less than .05). Apart from hyperglycemia, which does not occur in humans, these results in sheep suggest that epidurally administered clonidine does not adversely affect the fetus and may be evaluated as an analgesic in obstetrics.

L213 ANSWER 39 OF 83 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 90341008 EMBASE
DOCUMENT NUMBER: 1990341008
TITLE: [The reflex sympathetic distrophia syndrome].
DISTROFIA SIMPATICA REFLEJA.
AUTHOR: Rodriguez J.; Pons M.
CORPORATE SOURCE: Servicio de Reumatologia, Hospital de Bellvitge-Princeps, Hospitalet de Llobregat, 08907 Barcelona, Spain
SOURCE: Revista Espanola de Reumatologia, (1990) 17/4 (137-143).
ISSN: 0304-4815 CODEN: RERMAW
COUNTRY: Spain
DOCUMENT TYPE: Journal; **General Review**
FILE SEGMENT: 031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: Spanish

L213 ANSWER 40 OF 83 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 91310139 EMBASE
DOCUMENT NUMBER: 1991310139
TITLE: Pain control with intrathecally and peridurally administered opioids and other drugs.
AUTHOR: Foldes F.F.
CORPORATE SOURCE: Department of Asnesthesiology, University of Miami, School of Medicine, P.O. Box 016370, Miami, FL 33101, United States
SOURCE: Anaesthesiologie und Reanimation, (1991) 16/5 (287-298).
ISSN: 0323-4983 CODEN: ANREDN
COUNTRY: Germany
DOCUMENT TYPE: Journal; **General Review**
FILE SEGMENT: 008 Neurology and Neurosurgery

[redacted]

037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: German

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=> fil capl; d que l104
FILE 'CAPLUS' ENTERED AT 14:10:20 ON 15 OCT 2001
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FILE COVERS 1947 - 15 Oct 2001  VOL 135 ISS 17
FILE LAST UPDATED: 14 Oct 2001  (20011014/ED)

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L13            1 SEA FILE=REGISTRY ABB=ON  GUANADREL/CN
L20            1 SEA FILE=REGISTRY ABB=ON  GUANAZODINE/CN
L25            1 SEA FILE=REGISTRY ABB=ON  GUANETHIDINE/CN
L26            1 SEA FILE=REGISTRY ABB=ON  GUANFACINE/CN
L27            1 SEA FILE=REGISTRY ABB=ON  GUANOCLOR/CN
L32            1 SEA FILE=REGISTRY ABB=ON  GUANOXAN/CN
L37            1 SEA FILE=REGISTRY ABB=ON  4205-90-7
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L55            1 SEA FILE=REGISTRY ABB=ON  IDAZOXAN/CN
L56            1 SEA FILE=CAPLUS ABB=ON  ATEPAMEZOLE/BI
L65         6917 SEA FILE=CAPLUS ABB=ON  L1 OR L2 OR L3 OR L37 OR L8 OR L13 OR
                 L20 OR L25 OR L26 OR L27 OR L32 OR L37
L66        22625 SEA FILE=CAPLUS ABB=ON  ANALGESICS/CT
L67         7931 SEA FILE=CAPLUS ABB=ON  ANALGESIA/CT
L69         3571 SEA FILE=CAPLUS ABB=ON  "HYPNOTICS AND SEDATIVES"/CT
L103        2463 SEA FILE=CAPLUS ABB=ON  (L53 OR L54 OR L55 OR L56)
L104          22 SEA FILE=CAPLUS ABB=ON  (L69 OR L66 OR L67) AND L103 AND L65
L214         807 SEA FILE=CAPLUS ABB=ON  REVERS?(8A)(ANALGES? OR SEDAT?)
L215           0 SEA FILE=CAPLUS ABB=ON  L104 AND L214
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Searched by Barb O'Bryen, STIC 308-4191

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L27            1 SEA FILE=REGISTRY ABB=ON  GUANOCLOR/CN
L32            1 SEA FILE=REGISTRY ABB=ON  GUANOXAN/CN
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L66        22625 SEA FILE=CAPLUS ABB=ON  ANALGESICS/CT
L67         7931 SEA FILE=CAPLUS ABB=ON  ANALGESIA/CT
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L79       127845 SEA FILE=CAPLUS ABB=ON  CANINE OR DOG#
L80        60811 SEA FILE=CAPLUS ABB=ON  FELINE OR CAT#
L81       202583 SEA FILE=CAPLUS ABB=ON  BOVINE OR COW# OR CATTLE
L82        16790 SEA FILE=CAPLUS ABB=ON  CAPRINE OR GOAT#
L83       214691 SEA FILE=CAPLUS ABB=ON  PORCINE OR PIG# OR SWINE OR HOG#
L84        88117 SEA FILE=CAPLUS ABB=ON  OVINE OR SHEEP OR RAM# OR EWE# OR
                 LAMB#
L103        2463 SEA FILE=CAPLUS ABB=ON  (L53 OR L54 OR L55 OR L56)
L104          22 SEA FILE=CAPLUS ABB=ON  (L69 OR L66 OR L67) AND L103 AND L65
L216           3 SEA FILE=CAPLUS ABB=ON  (L78 OR L79 OR L80 OR L81 OR L82 OR
                 L83 OR L84) AND L104


=> fil medl; d que l131; d que l135
FILE 'MEDLINE' ENTERED AT 14:13:56 ON 15 OCT 2001

 FILE LAST UPDATED: 11 OCT 2001 (20011011/UP).  FILE COVERS 1958 TO DATE.

 On April 22, 2001, MEDLINE was reloaded.  See HELP RLOAD for details.

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 MEDLINE is now updated 4 times per week.  A new current-awareness alert
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 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH·2001 vocabulary.  Enter HELP THESAURUS for details.

 The OLDMEDLINE file segment now contains data from 1958 through 1965.
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 Basic Index.  See HELP SFIELDS for details.

 THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE
 SUBSTANCE IDENTIFICATION.


L105         296 SEA FILE=MEDLINE ABB=ON  GUANABENZ/CT
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L106      10194 SEA FILE=MEDLINE ABB=ON  CLONIDINE/CT
L107       2968 SEA FILE=MEDLINE ABB=ON  GUANETHIDINE/CT
L108        382 SEA FILE=MEDLINE ABB=ON  GUANFACINE/CT
L109         28 SEA FILE=MEDLINE ABB=ON  GUANOXABENZ OR HYDROXYGUANABENZ
L110         26 SEA FILE=MEDLINE ABB=ON  GUANACLINE OR CYCLAZENINE
L111         37 SEA FILE=MEDLINE ABB=ON  GUANADREL
L112         10 SEA FILE=MEDLINE ABB=ON  GUANAZODINE OR EGYT 739 OR SANEG!T
L113         11 SEA FILE=MEDLINE ABB=ON  GUANOCLOR OR GUANOCHLOR?
L114         80 SEA FILE=MEDLINE ABB=ON  GUANOXAN#
L117      17840 SEA FILE=MEDLINE ABB=ON  ANALGESIA+NT/CT
L118      18425 SEA FILE=MEDLINE ABB=ON  ANALGESICS/CT
L119       8724 SEA FILE=MEDLINE ABB=ON  "HYPNOTICS AND SEDATIVES"/CT
L120        615 SEA FILE=MEDLINE ABB=ON  (L105 OR L106 OR L107 OR L108 OR L109
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L122      36479 SEA FILE=MEDLINE ABB=ON  HORSES/CT
L123     677894 SEA FILE=MEDLINE ABB=ON  DOGS/CT OR CATS/CT OR CATTLE/CT OR
               GOATS/CT OR SWINE+NT/CT OR SHEEP/CT OR L122
L128       5210 SEA FILE=MEDLINE ABB=ON  YOHIMBINE/CT OR IDAZOXAN/CT
L129       1456 SEA FILE=MEDLINE ABB=ON  RAUWOLSCINE OR AT!PAMEZOLE OR MPV
               1248 OR CORYNANTHIDINE
L130         72 SEA FILE=MEDLINE ABB=ON  L120 AND (L128 OR L129)
L131          6 SEA FILE=MEDLINE ABB=ON  L123 AND L130



L105        296 SEA FILE=MEDLINE ABB=ON  GUANABENZ/CT
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L107       2968 SEA FILE=MEDLINE ABB=ON  GUANETHIDINE/CT
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L109         28 SEA FILE=MEDLINE ABB=ON  GUANOXABENZ OR HYDROXYGUANABENZ
L110         26 SEA FILE=MEDLINE ABB=ON  GUANACLINE OR CYCLAZENINE
L111         37 SEA FILE=MEDLINE ABB=ON  GUANADREL
L112         10 SEA FILE=MEDLINE ABB=ON  GUANAZODINE OR EGYT 739 OR SANEG!T
L113         11 SEA FILE=MEDLINE ABB=ON  GUANOCLOR OR GUANOCHLOR?
L114         80 SEA FILE=MEDLINE ABB=ON  GUANOXAN#
L119       8724 SEA FILE=MEDLINE ABB=ON  "HYPNOTICS AND SEDATIVES"/CT
L128       5210 SEA FILE=MEDLINE ABB=ON  YOHIMBINE/CT OR IDAZOXAN/CT
L129       1456 SEA FILE=MEDLINE ABB=ON  RAUWOLSCINE OR AT!PAMEZOLE OR MPV
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L135         16 SEA FILE=MEDLINE ABB=ON  L119 AND (L105 OR L106 OR L107 OR
               L108 OR L109 OR L110 OR L111 OR L112 OR L113 OR L114) AND
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=> d que l218
L105        296 SEA FILE=MEDLINE ABB=ON  GUANABENZ/CT
L106      10194 SEA FILE=MEDLINE ABB=ON  CLONIDINE/CT
L107       2968 SEA FILE=MEDLINE ABB=ON  GUANETHIDINE/CT
L108        382 SEA FILE=MEDLINE ABB=ON  GUANFACINE/CT
L109         28 SEA FILE=MEDLINE ABB=ON  GUANOXABENZ OR HYDROXYGUANABENZ
L110         26 SEA FILE=MEDLINE ABB=ON  GUANACLINE OR CYCLAZENINE
L111         37 SEA FILE=MEDLINE ABB=ON  GUANADREL
L112         10 SEA FILE=MEDLINE ABB=ON  GUANAZODINE OR EGYT 739 OR SANEG!T
L113         11 SEA FILE=MEDLINE ABB=ON  GUANOCLOR OR GUANOCHLOR?
L114         80 SEA FILE=MEDLINE ABB=ON  GUANOXAN#
L128       5210 SEA FILE=MEDLINE ABB=ON  YOHIMBINE/CT OR IDAZOXAN/CT
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L218          5 SEA FILE=MEDLINE ABB=ON  L217 AND (L105 OR L106 OR L107 OR
               L108 OR L109 OR L110 OR L111 OR L112 OR L113 OR L114) AND
               (L128 OR L129)
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Searched by Barb O'Bryen, STIC 308-4191

[redacted]

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=> s (l131 or l135 or l218) not l210
L219        18 (L131 OR L135 OR L218) NOT (L210)
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previously printed

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=> fil embase; d que l153; d que l159
FILE 'EMBASE' ENTERED AT 14:15:34 ON 15 OCT 2001
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 FILE COVERS 1974 TO 11 Oct 2001 (20011011/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
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L136      23010 SEA FILE=EMBASE ABB=ON  GUANABENZ/CT OR GUANABENZ ACETATE/CT
                OR GUANOXABENZ/CT OR CLONIDINE/CT OR CLONIDINE DERIVATIVE/CT
L137       7633 SEA FILE=EMBASE ABB=ON  GUANACLINE/CT OR GUANADREL/CT OR
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                /CT
L138        200 SEA FILE=EMBASE ABB=ON  GUANOXAN/CT
L139      11308 SEA FILE=EMBASE ABB=ON  YOHIMBINE/CT OR YOHIMBINE DERIVATIVE/CT
                 OR RAUWOLSCINE/CT OR IDAZOXAN/CT
L140        370 SEA FILE=EMBASE ABB=ON  ATIPAMEZOLE/CT
L142      36020 SEA FILE=EMBASE ABB=ON  ANALGESIA+NT/CT
L143      13092 SEA FILE=EMBASE ABB=ON  SEDATION/CT
L144        906 SEA FILE=EMBASE ABB=ON  HYPNOTIC SEDATIVE AGENT/CT
L145      17921 SEA FILE=EMBASE ABB=ON  ANALGESIC AGENT/CT
L154        953 SEA FILE=EMBASE ABB=ON  (L136 OR L137 OR L138)(L)IT/CT
L155        819 SEA FILE=EMBASE ABB=ON  (L139 OR L140)(L)IT/CT
L158        101 SEA FILE=EMBASE ABB=ON  L154/MAJ AND L155/MAJ
L159         10 SEA FILE=EMBASE ABB=ON  L158 AND (L142 OR L143 OR L144 OR
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— Subheading IT = drug interaction

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L137       7633 SEA FILE=EMBASE ABB=ON  GUANACLINE/CT OR GUANADREL/CT OR
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L138        200 SEA FILE=EMBASE ABB=ON  GUANOXAN/CT
L139      11308 SEA FILE=EMBASE ABB=ON  YOHIMBINE/CT OR YOHIMBINE DERIVATIVE/CT
                 OR RAUWOLSCINE/CT OR IDAZOXAN/CT
L140        370 SEA FILE=EMBASE ABB=ON  ATIPAMEZOLE/CT
L220        893 SEA FILE=EMBASE ABB=ON  REVERS?(8A)(ANALGES? OR SEDAT?)
L221          7 SEA FILE=EMBASE ABB=ON  L220 AND (L136 OR L137 OR L138) AND
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L137       7633 SEA FILE=EMBASE ABB=ON  GUANACLINE/CT OR GUANADREL/CT OR
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                /CT
L138        200 SEA FILE=EMBASE ABB=ON  GUANOXAN/CT
L139      11308 SEA FILE=EMBASE ABB=ON  YOHIMBINE/CT OR YOHIMBINE DERIVATIVE/CT
                 OR RAUWOLSCINE/CT OR IDAZOXAN/CT
L140        370 SEA FILE=EMBASE ABB=ON  ATIPAMEZOLE/CT
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L142      36020 SEA FILE=EMBASE ABB=ON  ANALGESIA+NT/CT
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L144        906 SEA FILE=EMBASE ABB=ON  HYPNOTIC SEDATIVE AGENT/CT
L145      17921 SEA FILE=EMBASE ABB=ON  ANALGESIC AGENT/CT
L146      10377 SEA FILE=EMBASE ABB=ON  HORSE/CT
L147     339127 SEA FILE=EMBASE ABB=ON  DOG/CT OR CAT/CT OR CATTLE/CT OR
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L223      19399 SEA FILE=EMBASE ABB=ON  L136/MAJ OR L137/MAJ OR L138/MAJ
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L227         11 SEA FILE=EMBASE ABB=ON  L223 AND L224 AND L226 AND L147


     (FILE 'EMBASE' ENTERED AT 14:15:34 ON 15 OCT 2001)
L228         27 S (L227 OR L159 OR L221) NOT L211
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previously printed

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=> fil wpids; d que l197; fil agricola caba biosis; d que l203;d que l208; d his l229
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L176         23 SEA FILE=WPIDS ABB=ON  GUANABENZ OR BR 750 OR WY 8678 OR
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L177        261 SEA FILE=WPIDS ABB=ON  CLONIDIN# OR CHLONIDIN# OR ST 155
L178          2 SEA FILE=WPIDS ABB=ON  GUANOXABENZ OR HYDROXYGUANABENZ
L179          0 SEA FILE=WPIDS ABB=ON  GUANACLIN# OR CYCLAZENIN#
L180          4 SEA FILE=WPIDS ABB=ON  GUANADREL OR GUANAZODIN# OR SANEG!T OR
                GUANOCLOR OR GUANOCHLOR? OR GUANOXAN#
L181         49 SEA FILE=WPIDS ABB=ON  GUANETHIDIN# OR ISMELIN# OR O!TADIN# OR
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L182        156 SEA FILE=WPIDS ABB=ON  ?YOHIMBINE? OR RAUWOLSCIN# OR CORYNANTH?
                 OR IDAZOXAN# OR RX 781094 OR AT!PAMEZOL# OR MPV 1248
L197          3 SEA FILE=WPIDS ABB=ON  (L176 OR L177 OR L178 OR L179 OR L180
                OR L181) AND L182


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L199 145539 SEA HORSE# OR EQUINE
L200 13905 SEA L1 OR L2 OR L3 OR L37 OR L8 OR L13 OR L20 OR L25 OR L26 OR L27 OR L32 OR L37
L201 17827 SEA (L176 OR L177 OR L178 OR L179 OR L180 OR L181)
L202 11350 SEA L182 OR L53 OR L54 OR L55 OR L56
L203 5 SEA (L200 OR L201) AND L202 AND L199

L1 1 SEA FILE=REGISTRY ABB=ON GUANABENZ/CN
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L180 4 SEA FILE=WPIDS ABB=ON GUANADREL OR GUANAZODIN# OR SANEG!T OR GUANOCLOR OR GUANOCHLOR? OR GUANOXAN#
L181 49 SEA FILE=WPIDS ABB=ON GUANETHIDIN# OR ISMELIN# OR O!TADIN# OR GUANFACIN# OR ESTULIC

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                 OR IDAZOXAN# OR RX 781094 OR AT!PAMEZOL# OR MPV 1248
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                 L27 OR L32 OR L37
L201      17827 SEA (L176 OR L177 OR L178 OR L179 OR L180 OR L181)
L202      11350 SEA L182 OR L53 OR L54 OR L55 OR L56
L204      62532 SEA ANALGES?
L205      18817 SEA SEDAT?
L207     322880 SEA REVERS?
L208          7 SEA (L204 OR L205)(8A) L207 AND (L200 OR L201) AND L202


     (FILE 'AGRICOLA, CABA, BIOSIS' ENTERED AT 14:20:56 ON 15 OCT 2001)
L229         11 S (L203 OR L208) NOT L206

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PROCESSING COMPLETED FOR L229
PROCESSING COMPLETED FOR L216
PROCESSING COMPLETED FOR L228
PROCESSING COMPLETED FOR L197
L230         51 DUP REM L219 L229 L216 L228 L197 (11 DUPLICATES REMOVED)
                ANSWERS '1-18' FROM FILE MEDLINE
                ANSWER '19' FROM FILE CABA
                ANSWERS '20-24' FROM FILE BIOSIS
                ANSWERS '25-27' FROM FILE CAPLUS
                ANSWERS '28-48' FROM FILE EMBASE
                ANSWERS '49-51' FROM FILE WPIDS

=> d ibib ab hitrn

L230 ANSWER 1 OF 51     MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:   95393127     MEDLINE
DOCUMENT NUMBER:    95393127   PubMed ID: 7664025
TITLE:              Histaminergic mechanisms in clonidine induced analgesia in
                    rat tail-flick test.
AUTHOR:             Arrigo-Reina R; Chiechio S
CORPORATE SOURCE:   Institute of Pharmacology and Pharmacognosy, Faculty of
                    Pharmacy, University of Catania, Italy.
SOURCE:             INFLAMMATION RESEARCH, (1995 Jan) 44 (1) 21-3.
                    Journal code: B8U; 9508160. ISSN: 1023-3830.
PUB. COUNTRY:       Switzerland
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previously printed

[redacted]

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 19951020
Last Updated on STN: 19951020
Entered Medline: 19951010

AB The role of neural histamine in clonidine-analgesia and in clonidine-induced potentiation of stress analgesia was studied. Pretreatment of rats with alpha-fluoromethylhistidine (FMH) (200 ug icv/rat; daily for five days) increased the analgesic effect of the alpha 2-agonist clonidine on the spinal reflex of the tail-flick test. Rats subjected to cold-restraint stress (30 min at 4 degrees C) showed increased latency compared to the unstressed rats. The analgesic efficacy of clonidine was significantly greater in rats subjected to cold-restraint with respect to unstressed rats. However, the inhibition of histamine biosynthesis by FMH significantly reduced cold-restraint analgesia in saline-controls, and consistently increased the analgesic efficacy of the alpha 2-agonist, showing a maximum latency. Yohimbine exhibited high affinity as an antagonist for alpha 2-receptors, inducing hyperalgesic effects and antagonizing clonidine analgesia and clonidine-induced potentiation of cold stress **analgesia**. In FMH-pretreated rats, yohimbine failed to **reverse** clonidine **analgesia** and did not block the increased **analgesic** efficacy of clonidine in cold-restrained FMH-pretreated rats. Results of this study suggest that inhibition of histamine release through alpha 2-adrenoceptors on histaminergic axons may contribute to the analgesic efficacy of systemically injected clonidine, also confirming that neural histaminergic pathways are implicated in the mediation of pain response in particular conditions of stress.

L230 ANSWER 2 OF 51 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 93305442 MEDLINE
DOCUMENT NUMBER: 93305442 PubMed ID: 8318322
TITLE: Partial reversal of the effects of extradural clonidine by oral yohimbine in postoperative patients.
AUTHOR: Liu N; Bonnet F; Delaunay L; Kermarec N; D'Honneur G
CORPORATE SOURCE: Departement d'Anesthesie Reanimation, Hopital Henri Mondor, Creteil, France.
SOURCE: BRITISH JOURNAL OF ANAESTHESIA, (1993 May) 70 (5) 515-8. Journal code: AUO; 0372541. ISSN: 0007-0912.
PUB. COUNTRY: ENGLAND: United Kingdom
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199308
ENTRY DATE: Entered STN: 19930813
Last Updated on STN: 19950206
Entered Medline: 19930803

AB Extradural clonidine produces analgesia, with sedation, hypotension and bradycardia, in postoperative patients. This study assessed if oral yohimbine would reverse these side effects. We studied 30 ASA I-II patients undergoing orthopaedic surgery. After operation they were allocated randomly to three groups to receive placebo, extradural clonidine 450 micrograms or extradural clonidine 450 micrograms plus oral yohimbine 16 mg. Pain score was measured on a visual analogue scale (VAS); sedation was assessed on a simple scale graded from 0 (awake and alert) to 3 (deeply sedated, awakening after tactile stimulations) and heart rate and arterial pressure were monitored for 5 h. Yohimbine **reversed** the **sedation** induced by extradural clonidine, but also shortened

the duration of analgesia (31 (SD 15) min, 186 (72) min and 126 (52) min in the placebo, extradural clonidine and extradural clonidine+yohimbine groups, respectively) ($P < 0.05$), and did not reduce the hypotension and bradycardia related to clonidine administration. These results suggest that alpha 2 adrenoceptors are mediators of the sedation induced by clonidine and that the haemodynamic effects are not related to stimulation of supraspinal alpha 2 receptors.

L230 ANSWER 3 OF 51 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 91171201 MEDLINE
DOCUMENT NUMBER: 91171201 PubMed ID: 2005587
TITLE: Differential contribution of descending serotonergic and noradrenergic systems to central Tyr-D-Ala2-Gly-NMePhe4-Gly-ol5 (DAMGO) and morphine-induced antinociception in mice.
AUTHOR: Arts K S; Holmes B B; Fujimoto J M
CORPORATE SOURCE: Research Service, Veterans Administration Medical Center, Milwaukee, Wisconsin.
CONTRACT NUMBER: DA00451 (NIDA)
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1991 Mar) 256 (3) 890-6.
Journal code: JP3; 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199104
ENTRY DATE: Entered STN: 19910512
Last Updated on STN: 20000303
Entered Medline: 19910424

AB Differences in antinociceptive (inhibition of tail-flick response) action of morphine and Tyr-D-Ala2-Gly-NMePhe4-ol5 (DAMGO) were demonstrated by intracerebroventricular (i.c.v.) administration of these agonists along with intrathecal (i.t.) administration of a variety of antagonists: yohimbine, methysergide, naloxone and nor-binaltorphimine. Intracerebroventricular morphine analgesia was antagonized by either i.t. yohimbine or methysergide, whereas i.c.v. DAMGO analgesia was only antagonized by i.t. methysergide. Thus, for i.c.v. morphine-induced analgesia, descending spinal noradrenergic and serotonergic systems were involved, whereas for DAMGO analgesia, only the serotonergic system was involved. The dose-response curve for i.c.v. morphine reached a plateau at high doses, whereas i.c.v. DAMGO analgesia peaked at 10 ng and then decreased thereafter, producing a bell-shaped dose-response curve. This decrement in **analgesic** response could be **reversed** by low doses of i.t. methysergide and i.t. pindolol. It was concluded that activation of serotonin-1 (5-HT1) receptors plays a role in the decrease in analgesia from high doses of DAMGO. Combinations of i.t. morphine with i.t. 5-HT or i.t. clonidine produced additive or greater analgesic responses. Combinations of i.t. DAMGO with i.t. 5-HT or i.t. clonidine produced less than additive interactions. Part of the latter responses appeared to be due to activation of 5-HT1 receptors; blockade of these receptors by pindolol enhanced i.t. DAMGO-induced analgesia. Morphine and DAMGO differ further because i.c.v. morphine activated a descending antianalgesic pathway mediated by spinal dynorphin A(1-17), whereas i.c.v. DAMGO at a high dose did not. Thus, morphine and DAMGO differ in their modes of antinociceptive action as measured by the tail-flick response.

L230 ANSWER 4 OF 51 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 87169280 MEDLINE
DOCUMENT NUMBER: 87169280 PubMed ID: 2435888
TITLE: Substance P-induced long-term blockade of spinal adrenergic **analgesia**: **reversal** by morphine and naloxone.
AUTHOR: Nance P W; Sawynok J

SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1987 Mar) 240 (3) 972-7.
Journal code: JP3; 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198704
ENTRY DATE: Entered STN: 19900303
Last Updated on STN: 19970203
Entered Medline: 19870427

AB Alpha agonists [noradrenaline (NA) and ST-91] inhibit the release of substance P (SP) from the spinal cord and block the biting, licking, scratching syndrome produced by intrathecal SP suggesting that these agents produce analgesia by an interaction with SP systems. In this study we determined the effect of a desensitizing regimen of SP (15 micrograms X 2 at a 30-min interval) on analgesia produced by intrathecal NA in the rat tail-flick test. When NA was injected immediately after the regimen or after a 90-minute delay, NA analgesia was blocked. This blockade persisted up to 11 days after exposure to SP. Exposure to a single dose of SP (15 or 30 micrograms) also blocked NA acutely, but the long-term blockade did not last as long. An identical effect was observed with ST-91. SP (15 micrograms X 2) potentiated the analgesic action of morphine acutely, but no interaction was observed 4 to 7 days later. Pretreatment with morphine and naloxone prevented the long-term blockade by SP. The effect of naloxone was not reversed by naltrexone suggesting that occupation of opiate receptors rather than an apparent agonist effect of naloxone caused the protection. Pretreatment with clonidine had only a slight effect on long-term blockade, but yohimbine was without effect. The present study describes a new long-term interaction between SP and alpha-2 agonists in the spinal cord. The mechanism(s) of the observed blockade by SP remains to be elucidated. However, there appears to be a functionally significant interaction between opiate and alpha-2 receptors in the spinal cord.

L230 ANSWER 5 OF 51 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 83297988 MEDLINE
DOCUMENT NUMBER: 83297988 PubMed ID: 6136932
TITLE: Neuropharmacological studies in rodents on the action of RX 781094, a new selective alpha 2-adrenoceptor antagonist.
AUTHOR: Dettmar P W; Lynn A G; Tulloch I F
SOURCE: NEUROPHARMACOLOGY, (1983 Jun) 22 (6) 729-37.
Journal code: NZB; 0236217. ISSN: 0028-3908.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198310
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19831021

AB Several neuropharmacological effects of RX 781094, a new selective alpha 2-adrenoceptor antagonist, have been investigated in rodents. In rats, RX 781094 (0.1-1.0 mg kg-1, i.v.) produced a rapid dose-related **reversal** of cortical EEG synchronisation and behavioural **sedation**, induced by clonidine or the more selective alpha 2-adrenoceptor agonist, **guanoxabenz**. The alpha 2-adrenoceptor antagonists yohimbine and mianserin were also effective in blocking **guanoxabenz**-induced EEG synchronisation but had a lower potency than did RX 781094. In specificity experiments, RX 781094 (1.0 mg kg-1, i.v.) failed to antagonise the EEG synchronisation and pronounced behavioural sedation induced by the CNS depressant sodium pentobarbitone (15 mg kg-1, i.v.). In mice, pretreatment (i.v. or p.o.) with RX 781094 inhibited in a dose-dependent way both **guanoxabenz**-induced

behavioural hypoactivity and clonidine-induced hypothermia. By itself, RX 781094 had no effect on the temperature of normal mice. In sleep-waking studies in rats, RX 781094 (0.1 and 1.0 mg kg-1, i.v.) had no measurable stimulant or depressant effect on the CNS, in contrast to (+)-amphetamine (1.0 mg kg-1, i.v.) which elicited marked CNS stimulation. These results support the conclusion that RX 781094 is a potent antagonist at central alpha 2-adrenoceptors.

L230 ANSWER 6 OF 51 MEDLINE
ACCESSION NUMBER: 1998197027 MEDLINE
DOCUMENT NUMBER: 98197027 PubMed ID: 9537677
TITLE: The alpha-2a noradrenergic agonist, guanfacine, improves delayed response performance in young adult rhesus monkeys.
AUTHOR: Franowicz J S; Arnsten A F
CORPORATE SOURCE: Section of Neurobiology, Yale University School of Medicine, New Haven, CT 06520-8001, USA.
SOURCE: PSYCHOPHARMACOLOGY, (1998 Mar) 136 (1) 8-14.
Journal code: QGI; 7608025. ISSN: 0033-3158.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980529
Last Updated on STN: 19980529
Entered Medline: 19980521

AB In aged monkeys with naturally occurring catecholamine depletion, alpha-2 adrenergic agonists such as guanfacine have repeatedly been shown to improve dorsolateral prefrontal cortical function, as assessed by the spatial delayed response task. Both low (0.0001-0.001 mg/kg) and high (0.5 mg/kg) but not intermediate (0.01-0.05 mg/kg) doses of guanfacine improve spatial working memory performance in aged animals. However, it is not known whether guanfacine would similarly improve performance in young animals. In the present study, the effects of guanfacine on delayed response performance were characterized in seven young adult rhesus monkeys. Low doses of guanfacine (0.0001-0.01 mg/kg) had no effect on task performance, while high doses of guanfacine (0.1-0.7 mg/kg) significantly improved task performance. The highest doses produced mild sedation that was independent of drug effects on delayed response. The most effective dose of guanfacine was challenged with the alpha-2 antagonist idazoxan (0.1 mg/kg). This dose of idazoxan had no effect on task performance when given alone. Consistent with an alpha-2 mechanism, idazoxan significantly decreased delayed response performance in guanfacine-treated animals. These results support the hypothesis that delayed response performance in young intact animals can be improved through actions at alpha-2 adrenergic receptors.

L230 ANSWER 7 OF 51 MEDLINE
ACCESSION NUMBER: 94315673 MEDLINE
DOCUMENT NUMBER: 94315673 PubMed ID: 7913727
TITLE: Effects of medetomidine on intestinal and colonic motility in the dog.
AUTHOR: Maugeri S; Ferre J P; Intorre L; Soldani G
CORPORATE SOURCE: Laboratory of Pharmacology, Faculty of Veterinary Medicine, University of Pisa, Italy.
SOURCE: JOURNAL OF VETERINARY PHARMACOLOGY AND THERAPEUTICS, (1994 Apr) 17 (2) 148-54.
Journal code: KCP; 7910920. ISSN: 0140-7783.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199408

[redacted]

ENTRY DATE: Entered STN: 19940905
Last Updated on STN: 20000303
Entered Medline: 19940822

AB The motor responses of the jejunum and colon to stimulation of alpha 2-adrenoceptors by medetomidine and clonidine were investigated in four dogs. In fasting dogs, medetomidine, at a dose rate of 30 micrograms/kg i.v., disrupted the migrating myoelectric complex (MMC) pattern of the small intestine for about 2 h. Similar, but shorter-lasting effects were also induced by clonidine (30 micrograms/kg i.v.) on the jejunum. The administration of alpha 2-agonists inhibited colonic motility in fasting dogs, although medetomidine-induced inhibition was preceded by a short period of increased muscle tone. All these effects were reversed by the alpha 2-antagonists **atipamezole** (0.15 mg/kg i.v.) and yohimbine (0.20 mg/kg i.v.). In fed dogs, medetomidine (30 micrograms/kg i.v.) induced a strong increase of the tone on the proximal colon, while the activity of the medium and distal colon was completely suppressed. Yohimbine (0.50 mg/kg i.v.) immediately restored the activity of the colon and induced a propagated giant contraction and defaecation by the animal. These data confirm the importance of alpha 2-adrenergic receptors in the control of intestinal and colonic motility in the dog.

L230 ANSWER 8 OF 51 MEDLINE
ACCESSION NUMBER: 92158140 MEDLINE
DOCUMENT NUMBER: 92158140 PubMed ID: 1686301
TITLE: Behavioral and receptor binding analysis of the alpha 2-adrenergic agonist, 5-bromo-6 [2-imidazoline-2-yl amino] quinoxaline (UK-14304): evidence for cognitive enhancement at an alpha 2-adrenoceptor subtype.
AUTHOR: Arnsten A F; Leslie F M
CORPORATE SOURCE: Section of Neuroanatomy, Yale Medical School, New Haven, CT 06510.
CONTRACT NUMBER: AG06036 (NIA)
NS19319 (NINDS)
SOURCE: NEUROPHARMACOLOGY, (1991 Dec) 30 (12A) 1279-89.
Journal code: NZB; 0236217. ISSN: 0028-3908.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199203
ENTRY DATE: Entered STN: 19920410
Last Updated on STN: 19970203
Entered Medline: 19920324

AB The ability of the alpha 2-agonists clonidine, B-HT920 (6-allyl-2-amino-5,6,7,8-tetrohydro-4H-thiazolo-[4,5-d]-azepine) and guanfacine to improve memory in aged monkeys has been related to their affinity to bind at a proposed **rauwolscine**-insensitive (Ri) subtype of alpha 2-adrenergic receptor, while their hypotensive and sedating effects have been related to affinity at a **rauwolscine** -sensitive site (Rs) (Arnsten et al., 1988). The present study examined the alpha 2-agonist UK-14304 (5-bromo-6 [2-imidazoline-2-yl amino] quinoxaline) for its binding characteristics in tissue from the brain of the rat and for its behavioral effects in aged monkeys. The drug UK-14304 was found to have slightly higher affinity for the Ri than the Rs site (Ki values of 138 and 245 nM, respectively), but was not as selective as the alpha 2-agonist guanfacine (Ki values of 23 and 340 nM, respectively). Consistent with this binding profile, very small doses of UK-14304 (0.00017-0.17 micrograms/kg) produced a reliable but modest improvement in memory in the aged monkeys (average improvement of 16.7% +/- 2.6% following an optimal dose). No hypotensive or sedating side effects were observed at these small doses. However, hypotension and sedation emerged rapidly when the dose was raised above 1.7 micrograms/kg and at the largest doses tested (50.0-100.0 micrograms/kg), hypotension was severe

(systolic pressure below 70 mm Hg) and the animals were too sedated to complete cognitive testing. The separation between doses that improved memory and those that produced hypotension and sedation was not as great for UK-14304 as it was for guanfacine, consistent with the greater selectivity of guanfacine for the Ri site. These results offer a fourth example whereby the ability of an alpha 2-agonist to improve cognitive function, without side effects, could be related to the relative affinities for the Ri and Rs sites.

L230 ANSWER 9 OF 51 MEDLINE
ACCESSION NUMBER: 92187824 MEDLINE
DOCUMENT NUMBER: 92187824 PubMed ID: 1686814
TITLE: Pharmacology of saccadic eye movements in man. 2. Effects of the alpha 2-adrenoceptor ligands idazoxan and clonidine.
AUTHOR: Glue P; White E; Wilson S; Ball D M; Nutt D J
CORPORATE SOURCE: Reckitt and Colman Psychopharmacology Unit, School of Medical Sciences, University Walk, UK.
SOURCE: PSYCHOPHARMACOLOGY, (1991) 105 (3) 368-73.
Journal code: QGI; 7608025. ISSN: 0033-3158.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 19920424
Last Updated on STN: 19970203
Entered Medline: 19920413

AB The effects of alpha 2-adrenoceptor agonists and antagonists on saccadic eye movements were studied in normal volunteers using the agonist clonidine and the antagonist idazoxan. Changes in blood pressure, heart rate, and several psychological self-ratings were also recorded. Clonidine produced marked slowing of peak saccade velocity, acceleration and deceleration, with deceleration affected more than acceleration, but had no effect on saccade error or latency measurements. In contrast, most saccade parameters were not altered by idazoxan, although fatigue effects were eliminated. Blood pressure, heart rate, and self ratings of alertness were increased by idazoxan and reduced by clonidine, with opposite effects noted on sedation self-ratings. There were no correlations between the clonidine-induced changes in saccade parameters and changes in self-ratings. Although the slowing of some saccade parameters by clonidine may imply that alpha 2-adrenoceptors are involved in control of saccades, it may also be due to sedation. Although alpha 2-adrenoceptor antagonists may abolish fatigue effects, they cannot increase them over baseline values.

L230 ANSWER 10 OF 51 MEDLINE
ACCESSION NUMBER: 89216579 MEDLINE
DOCUMENT NUMBER: 89216579 PubMed ID: 2565389
TITLE: Antidiarrheal activity of alpha-2 adrenoceptor agonist SK&F 35886.
AUTHOR: Fondacaro J D; McCafferty G P; Kolpak D C; Smith P L
CORPORATE SOURCE: Department of Pharmacology, Smith Kline and French Laboratories, Philadelphia, Pennsylvania.
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1989 Apr) 249 (1) 221-8.
Journal code: JP3; 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198906

ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19950206
Entered Medline: 19890601

AB Alpha-2 adrenoceptor agonists exhibit antidiarrheal activity in animal models and in humans. However, hypotensive and sedative side effects seriously limit the use of these agents to treat diarrhea. SK&F 35886 (2,6-dimethyl phenylamino imidazoline) is an alpha-2 adrenoceptor agonist with little central nervous system activity. In Ussing chamber preparations of rabbit ileum, SK&F 35886 produces a concentration-dependent decrease in basal short-circuit current (Isc) (EC50 0.2 microM) that is dependent on the presence of mucosal HCO3. This concentration-response curve is shifted to the right of **rauwolscine**, increasing the EC50 to 30 microM. Prazosin had no effect on this response. Flux studies indicate that SK&F 35886 increases net Cl absorption and enhances HCO3 absorption without altering net Na flux. After PGE2 stimulation of Isc, SK&F 35886, applied either serosally or mucosally, immediately returns the Isc to base line. This effect is due to a reversal of the PGE2-induced inhibition of Na and Cl absorption. In vivo SK&F 35886 dose-dependently inhibits PGE2-induced enteropooling when given orally (ED50 approximately 31 micrograms/kg). This effect is attenuated significantly by **rauwolscine** (1.0 micrograms/kg s.c.). In cecectomized rats, SK&F 35886 abolishes PGE2-induced diarrhea within 1 hr after oral administration of the drug. SK&F 35886 (500 micrograms/kg p.o.) did not alter hexobarbital sleep time or elicit piloerection or lethargy, whereas clonidine (37.3 micrograms/kg p.o.) significantly enhanced hexobarbital sleep time. These results illustrate the ability of a peripheral acting alpha-2 agonist to promote absorption and inhibit secretion and diarrhea in the mammalian intestine.

L230 ANSWER 11 OF 51 MEDLINE
ACCESSION NUMBER: 89036353 MEDLINE
DOCUMENT NUMBER: 89036353 PubMed ID: 2903226
TITLE: The alpha-2 adrenergic agonist guanfacine improves memory in aged monkeys without sedative or hypotensive side effects: evidence for alpha-2 receptor subtypes.
AUTHOR: Arnsten A F; Cai J X; Goldman-Rakic P S
CORPORATE SOURCE: Section of Neuroanatomy, Yale Medical School, New Haven, Connecticut 06510.
CONTRACT NUMBER: AG06036 (NIA)
MH38546 (NIMH)
SOURCE: JOURNAL OF NEUROSCIENCE, (1988 Nov) 8 (11) 4287-98.
Journal code: JDF; 8102140. ISSN: 0270-6474.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198812
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19881222

AB The present study attempted to identify an alpha-2 agonist that could improve working memory in aged nonhuman primates without the marked hypotensive and sedative side effects produced by clonidine. Toward this end, the hypotensive, sedative, and memory-altering properties of the alpha-2 adrenergic agonists, B-HT920 and guanfacine, were compared with clonidine's effects in 9 aged rhesus monkeys. Memory capacity was assessed by a variable delay, spatial delayed response paradigm that requires the animal to remember information over short temporal intervals and to update this information on every trial. B-HT920 was found to produce a dose-response profile qualitatively similar to, but weaker than, clonidine: low doses impaired memory and began to lower blood pressure and produce sedation, while high doses improved memory. In contrast, guanfacine produced a dose-response profile opposite to that seen with

clonidine: low doses improved memory without inducing hypotension or sedation, while the memory-impairing, hypotensive, and sedating properties of the drug were observed at higher doses. The potency of the 3 agonists to lower blood pressure was clonidine = B-HT920 greater than guanfacine; sedation was affected in the order clonidine greater than B-HT920 greater than guanfacine; for memory impairment, as measured by performance on the delayed response task, the rank order potency was clonidine greater than B-HT920 greater than guanfacine, while for memory improvement it was guanfacine greater than clonidine greater than B-HT920. These differences in rank order potency are consistent with the recent proposal of alpha-2 receptor subtypes, a **rauwolscine**-sensitive site (Rs) that binds clonidine greater than B-HT920 greater than guanfacine and a **rauwolscine**-insensitive site (Ri) that binds guanfacine greater than clonidine greater than B-HT920 (Boyajian and Leslie, 1987). The data suggest that the hypotensive, sedating, and memory-impairing effects of alpha-2 agonists may be due to actions at one subtype of receptor (Rs), while the memory-enhancing effects of these drugs may result from actions at another alpha-2 receptor subtype, the Ri site. The ability of low doses of guanfacine to improve memory without inducing hypotension or sedation indicates that this agonist may be an excellent candidate for treating memory disorders in man.

L230 ANSWER 12 OF 51 MEDLINE
ACCESSION NUMBER: 88320803 MEDLINE
DOCUMENT NUMBER: 88320803 PubMed ID: 2901123
TITLE: Behavioral evidence for the role of noradrenaline in putative anxiolytic and sedative effects of benzodiazepines.
AUTHOR: Yang X M; Luo Z P; Zhou J H
CORPORATE SOURCE: Institute of Pharmacology and Toxicology, Beijing, People's Republic of China.
SOURCE: PSYCHOPHARMACOLOGY, (1988) 95 (2) 280-6.
Journal code: QGI; 7608025. ISSN: 0033-3158.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198810
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19950206
Entered Medline: 19881004

AB The effects of clonidine on the antianxiety and sedation of benzodiazepines (BZD) were assessed respectively in rats trained in a two-lever diazepam cue discrimination procedure and in single-lever fixed-ratio (FR) water-reinforced performance. Clonidine (10-60 micrograms/kg) significantly shifted to the left the dose-effect curves of diazepam in the discrimination paradigm. This treatment also shifted generalization dose-effect curves of the diazepam cue to chlordiazepoxide and CL 218,872 to the left in the drug discrimination procedure. The diazepam cue was antagonized in a dose-related manner by Ro 15-1788, but not by bicuculline. Clonidine also potentiated the rate-decreasing effects of diazepam on the FR schedule when the dose of diazepam was increased to 0.3 mg/kg, but not the milder rate-decreasing effect of CL 218,872 until the dose of CL 218,872 was increased to 10 mg/kg. The potentiating effects of clonidine on the stimulus control and depression of diazepam were antagonized by yohimbine. Yohimbine (1.0 mg/kg) also significantly shifted the dose-effect curve of diazepam cue to the right. Bicuculline (3 mg/kg) completely antagonized the rate-decreasing effect of diazepam (1 mg/kg), but significantly potentiated the rate-suppressant effect of clonidine (10 micrograms/kg). These results suggest that the central noradrenaline (NA) system may be involved not only in the antianxiety, but also the sadative action of BZD. The nature of NA involvement in relation to the different subtypes of BZD receptors requires further exploration.

[redacted]

L230 ANSWER 13 OF 51 MEDLINE
ACCESSION NUMBER: 87143100 MEDLINE
DOCUMENT NUMBER: 87143100 PubMed ID: 3029520
TITLE: Evidence for the involvement of alpha-2 adrenoceptors in the sedation but not REM sleep inhibition by clonidine in the rat.
AUTHOR: Makela J P; Hilakivi I T
SOURCE: MEDICAL BIOLOGY, (1986) 64 (6) 355-60.
Journal code: LOY; 0417300. ISSN: 0302-2137.
PUB. COUNTRY: Finland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198704
ENTRY DATE: Entered STN: 19900303
Last Updated on STN: 19970203
Entered Medline: 19870406

AB Rats with implanted electrodes for recording of EEG and EMG underwent 12-h recordings during the light period starting after i.p. injections of clonidine (0.1 mg/kg) alone or in combination with different alpha-adrenoceptor antagonists. Clonidine increased the proportion of time the rats spent in the drowsy stage of wakefulness which corresponds to behavioural sedation and inhibited both deep slow wave sleep and REM sleep for 6-9 hours. The amount of active wakefulness or light slow wave sleep were unaffected by clonidine. Yohimbine (1 mg/kg) reversed the increase in drowsy wakefulness by clonidine and increased active wakefulness without affecting sleep. Phentolamine (10 mg/kg) was ineffective against clonidine. Phenoxybenzamine (20 mg/kg) accentuated the sedative effect and prolonged the REM sleep inhibiting effect of clonidine. Prazosin (3 mg/kg) prolonged both the drowsy stage inducing and deep slow wave plus REM sleep inhibiting effects of clonidine. These electrophysiological results support the view that the sedative effect of clonidine in the rat is mediated by alpha-2 adrenoceptors, whereas in this species other mechanisms, possibly another population of alpha-2 receptors, may be involved in the clonidine-induced suppression of deep slow wave sleep and REM sleep.

L230 ANSWER 14 OF 51 MEDLINE
ACCESSION NUMBER: 86121459 MEDLINE
DOCUMENT NUMBER: 86121459 PubMed ID: 2868483
TITLE: Imidazole has similar behavioural effects to yohimbine.
AUTHOR: Ferrari F; Martinelli R; Baggio G
SOURCE: PSYCHOPHARMACOLOGY, (1986) 88 (1) 58-62.
Journal code: QGI; 7608025. ISSN: 0033-3158.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198603
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19950206
Entered Medline: 19860310

AB A number of animal behavioural models were used to study the activity of imidazole (IMID) on the central nervous system. IMID antagonized in a dose-related fashion penile erections (PE) as well as stretching and yawning (SY) elicited in male rats by B-HT 920, an alpha 2 and dopamine (DA) autoreceptor agonist. Inhibition of B-HT 920-induced PE and SY was also exhibited by haloperidol, a DA receptor blocker, and yohimbine, but not by prazosin, alpha 2 and alpha 1 receptor antagonists respectively. Moreover IMID behaved similarly to yohimbine in: 1) counteracting clonidine-induced hypothermia in mice; 2) antagonizing sedation and sleep induced by clonidine and B-HT 920 in chicks, while haloperidol was

ineffective. When administered to sexually active rats before the copulatory test, IMID at low doses, significantly altered some aspects of mating, a result which is interpretable in terms of enhanced sexual arousal and resembling the aphrodisiac effect reported for yohimbine. The neurochemical mechanisms involved in these effects are discussed.

L230 ANSWER 15 OF 51 MEDLINE
ACCESSION NUMBER: 86049668 MEDLINE
DOCUMENT NUMBER: 86049668 PubMed ID: 2865936
TITLE: Antagonistic effects of S9871 or (imidazolinyl-2)-2-dihydro 2,3 benzofurane and its stereoisomers on some central and peripheral actions of alpha 2-agonists.
AUTHOR: Joly G; Mouille P; Schmitt H
SOURCE: ARCHIVES INTERNATIONALES DE PHARMACODYNAMIE ET DE THERAPIE, (1985 Oct) 277 (2) 180-91.
Journal code: 7EK; 0405353. ISSN: 0003-9780.
PUB. COUNTRY: Belgium
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198512
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19970203
Entered Medline: 19851218

AB (+/-) and (+), but not (-) S9871 are new alpha 2-adrenoceptor selective antagonists. The effect of the racemic mixture and of the stereoisomers on cardiovascular and sedative responses to clonidine have been studied in rats and chickens, respectively. Blockade of central alpha 2-adrenoceptors was also measured as a recovery of the sympathoinhibitory effect induced by intravenous administration of B-HT 933 (azepexole). The potency profiles of these agents established in the central nervous system were confirmed in studies using the vas deferens in situ in the pithed rat. (+/-) and (+) S9871 blocked and antagonized some centrally mediated effects of clonidine such as the depressor response to both intravenous and intracerebroventricular administration. However, the return of arterial pressure to the control value, after intravenous administration of (-) S9871, does not result from an antagonistic action on alpha 2-adrenoceptors, since the depressor effects of clonidine were not blocked, but could be explained by alpha-agonistic properties of (-) S9871. (+/-) and (+) S9871 also blocked and antagonized the hypotensive and bradycardic action induced by intravenous administration of B-HT 933. The loss of the righting reflex induced by clonidine in the chicken was prevented by (+/-) and (+) S9871, as shown by a shift of the dose-response curve to clonidine to the right by both agents; on the contrary, (-) S9871 potentiated the sedation induced by clonidine. In the pithed rat, intravenously administered (+/-) and (+) S9871 fully antagonized the inhibitory effects of clonidine on the electrically induced contractions of the vas deferens. These observations are consistent with a selective alpha 2-adrenoceptors antagonistic effect of (+/-) and (+) S9871 at central and peripheral alpha 2-adrenoceptors.

L230 ANSWER 16 OF 51 MEDLINE
ACCESSION NUMBER: 84164474 MEDLINE
DOCUMENT NUMBER: 84164474 PubMed ID: 6142941
TITLE: A study of the selectivity and potency of **rauwolscine**, RX 781094 and RS 21361 as antagonists of alpha-1 and alpha-2 adrenoceptors.
AUTHOR: Timmermans P B; Qian J Q; Ruffolo R R Jr; van Zwieten P A
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1984 Mar) 228 (3) 739-48.
Journal code: JP3; 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

[redacted]

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198405
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19840502

AB In a comparative study using various in vivo and in vitro models, the alpha-1/alpha-2 adrenoceptor blocking potencies and selectivities were quantitatively assessed for the purported alpha-2 adrenoceptor selective antagonists **rauwolscine**, RX 781094 and RS 21361. In pithed normotensive rats, RX 781094 showed direct agonist activity at postjunctional alpha-1 and alpha-2 adrenoceptors and had an indirect tachycardic effect. RS 21361 exhibited but minor actions on diastolic pressure and did not influence heart rate. **Rauwolscine**, RX 781094 and RS 21361 caused rightward parallel displacements of the log dose-response curve to the increase in diastolic pressure of methoxamine (alpha-1 agonist) and B-HT 920 (alpha-2 agonist) as well as to the B-HT 920-induced reduction in stimulation-evoked tachycardia. Schild plots afforded straight lines with slopes not significantly different from unity. **Rauwolscine** was more potent than RX 781094 in blocking these alpha-2 adrenoceptors in vivo, whereas both compounds were equipotent at alpha-1 adrenoceptors. RS 21361 possessed moderate in vivo blocking potencies at either subtype. All three antagonists had high blocking selectivity for alpha-2 adrenoceptors in vivo. **Rauwolscine** was found about 25 times more selective than RX 781094 and 2 times more selective than RS 21361. RX 781094 was approximately 3 times more effective than **rauwolscine** in antagonizing the centrally mediated alpha-2 adrenoceptor-induced hypotension and sedation of clonidine in rats and mice, respectively.(ABSTRACT TRUNCATED AT 250 WORDS)

L230 ANSWER 17 OF 51 MEDLINE
ACCESSION NUMBER: 85003830 MEDLINE
DOCUMENT NUMBER: 85003830 PubMed ID: 6090162
TITLE: Clonidine and yohimbine separate the sedation and the ptosis caused by cholecystokinin octapeptide and ceruletide.
AUTHOR: Zetler G
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1984 Jul 13) 102 (2) 333-40.
Journal code: EN6; 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198411
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19841109

AB The central depressant effects of ceruletide (CER, 0.04 mg/kg s.c.) and cholecystokinin octapeptide (CCK-8, 0.25 mg/kg s.c.) were compared with those of clonidine (0.04 mg/kg s.c.). At doses that were nearly equipotent with respect to motor inhibition (catalepsy, reduction in ambulation and exploratory rearing), only the peptides produced ptosis. Yohimbine (1 mg/kg s.c., 30 min) antagonized the effect of clonidine but not of the peptides. Clonidine (0.07-0.2 mg/kg s.c., 30 min) antagonised the ptotic action of the peptides, and this effect was abolished by yohimbine (0.2-1 mg/kg i.p.) but resistant to haloperidol (0.05 and 0.15 mg/kg i.p.). These results separate the behavioural effects of the peptides from those of clonidine and also the ptotic effect of the peptides from their effect on motor activity. The antiptotic effect of clonidine may originate from activated adrenergic autoreceptors.

L230 ANSWER 18 OF 51 MEDLINE
ACCESSION NUMBER: 73257864 MEDLINE
DOCUMENT NUMBER: 73257864 PubMed ID: 4147334
TITLE: A further attempt to characterize sedative receptors activated by clonidine in chickens and mice.
AUTHOR: Delbarre B; Schmitt H
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1973 Jun) 22 (3) 355-9. Journal code: EN6; 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197311
ENTRY DATE: Entered STN: 19900310
Last Updated on STN: 19950206
Entered Medline: 19731116

L230 ANSWER 19 OF 51 CABA COPYRIGHT 2001 CABI
ACCESSION NUMBER: 94:20819 CABA
DOCUMENT NUMBER: 942201778
TITLE: Prejunctional alpha 2-adrenoceptors inhibit acetylcholine release from cholinergic nerves in **equine** airways
AUTHOR: Yu, M.; Wang, Z.; Robinson, E.
CORPORATE SOURCE: Department of Large Animal Clinical Sciences, Michigan State University, East Lansing, MI 48824, USA.
SOURCE: American Journal of Physiology, (1993) Vol. 265, No. 6, part 1, pp. L565-L580. 46 ref.
ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To determine the presence and function of alpha 2-adrenoceptors on cholinergic nerves innervating **horse** airway smooth muscle, the effects of some alpha 2-adrenoceptor agents on contractions of and acetylcholine (ACh) release from **equine** airway smooth muscle preparations were studied. Muscle contractions were elicited by either electrical field stimulation (EFS) or exogenous ACh. ACh release was induced by EFS and measured by high-pressure liquid chromatography and electrochemical detection. The alpha 2-adrenoceptor agonists **clonidine** (10-7 to 10-5 M) and UK-14,304 (10-8 to 10-6 M) concentration dependently inhibited ACh release and the contractile response to EFS but not the response to exogenous ACh. This inhibition was attenuated by the alpha 2-adrenoceptor antagonists **yohimbine** and **idazoxan** but not by the alpha 1-adrenoceptor antagonist prazosin. It is concluded that alpha 2-adrenoceptors exist on cholinergic nerves innervating **equine** airway smooth muscle, and activation of these receptors inhibits cholinergic neurotransmission. The observation that **yohimbine** alone had little effect on the contractile response to EFS suggests that, under these experimental conditions, endogenous norepinephrine had no influence on tracheal cholinergic neurotransmission via prejunctional alpha 2-adrenoceptors.

L230 ANSWER 20 OF 51 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 5
ACCESSION NUMBER: 1987:300985 BIOSIS
DOCUMENT NUMBER: BA84:31017
TITLE: EPIDURAL **CLONIDINE** PRODUCES ANTINOCICEPTION BUT NOT HYPOTENSION IN SHEEP.
AUTHOR(S): EISENACH J C; DEWAN D M; ROSE J C; ANGELO J M
CORPORATE SOURCE: DEP. ANESTHESIA, WAKE FOREST UNIV., BOWMAN GRAY SCH. MED., WINSTON-SALEM, N.C. 27103.
SOURCE: ANESTHESIOLOGY, (1987) 66 (4), 496-501.
CODEN: ANESAV. ISSN: 0003-3022.

FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Intrathecally administered **clonidine** produces analgesia, but also produces hypotension. To assess the effects of epidural administration, the authors inserted lumbar epidural catheters in seven nonpregnant ewes, and injected, on separate days, **clonidine** (50-750 mcg), morphine (5-10 mg), and a **clonidine**-morphine combination (**clonidine** 150 mcg + morphine 5 mg). **Clonidine** produced dose-dependent antinociception and sedation, with the lowest maximally effective antinociceptive dose being 300 mcg. Morphine produced less intense antinociception than **clonidine**, and did not potentiate **clonidine**'s effect. Antinociception, but not **sedation**, following **clonidine** injection was **reversed** by epidural injection of the .alpha.2-adrenergic antagonist, **idazoxan**. Epidurally administered naloxone and prazosin did not reverse **clonidine**'s antinociceptive efect, nor did intravenously administered **idazoxan**. Epidurally administered **clonidine** did not decrease blood pressure or heart rate or affect arterial blood gas tensions or spinal cord histology. These data suggest that epidurally administered **clonidine** produces analgesia by a local, .alpha.2-adrenergic mechanism. In sheep, epidurally administered **clonidine** does not produce hypotension.

L230 ANSWER 21 OF 51 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:265967 BIOSIS
DOCUMENT NUMBER: PREV199799572570
TITLE: Prejunctional alpha-2-adrenoceptors inhibit nitrergic neurotransmission in **horse** penile resistance arteries.
AUTHOR(S): Simonsen, Ulf (1); Prieto, Dolores; Hernandez, Medardo; De Tejada, Inigo Saenz; Garcia-Sacristan, Albino
CORPORATE SOURCE: (1) Dep. Pharmacol., Aarhus Univ., 8000 Aarhus C Denmark
SOURCE: Journal of Urology, (1997) Vol. 157, No. 6, pp. 2356-2360. ISSN: 0022-5347.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Purpose: To study the influence of a-adrenergic stimuli on non-adrenergic non-cholinergic (NANC) neurogenic relaxation in isolated **horse** penile resistance arteries. Materials and Methods: Deep intracavernous penile arteries with an internal lumen diameter of 200-500 mu-m, isolated from the corpus cavernosum of young **horses**, were mounted in microvascular myographs for isometric tension recording and electrical field stimulation (EFS) of autonomic nerve terminals. Results: In the presence of **guanethidine** (10-5 M) and atropine (10-7 M) tone of the arteries was raised by the thromboxane analogue, U46619. EFS (1, 4 and 32 Hz) induced frequency-dependent relaxations, which were abolished in the presence of tetrodotoxin, while N-G-nitro-L-arginine (L-NOARG, 10-4 M) abolished the relaxations to EFS at 1 Hz, and significantly reduced the relaxations at 4 Hz and 32 Hz by 82.5 +- 10.2% and 52.9 +- 4.7%, respectively (n = 6). EFS induced relaxations of a similar magnitude in penile arteries contracted with U46619 or the alpha-1-adrenoceptor agonist, phenylephrine, while the alpha-2-adrenoceptor agonist, BHT920 (10-6 M), produced an inhibitory effect on the EFS-evoked relaxations which was inversely related to the stimulus frequency (1, 4 and 32 Hz). BHT920 had no effect on the relaxations induced by exogenous nitric oxide (NO), added as acidified sodium nitrite (10-6-10-3 M). The inhibitory effect of BHT920 on NANC relaxations was reversed by 10-7 M **rauwolscine**. Conclusion: These results suggest that the release of a NANC neurotransmitter primarily thought to be NO is inhibited by stimulation of prejunctional alpha-2-adrenoceptors in **horse** penile resistance arteries.

L230 ANSWER 22 OF 51 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1995:213609 BIOSIS
DOCUMENT NUMBER: PREV199598227909
TITLE: Catecholamine affects acetylcholine release in trachea: alpha-2-mediated inhibition and beta-2-mediated augmentation.
AUTHOR(S): Zhang, Xiang-Yang; Robinson, N. Edward (1); Wang, Zhao-Wen; Lu, Min-Chi
CORPORATE SOURCE: (1) Dep. Large Animal Clinical Sci., Vet. Medicine Cent., Michigan State Univ., East Lansing, MI 48824-1314 USA
SOURCE: American Journal of Physiology, (1995) Vol. 268, No. 3 PART 1, pp. L368-L373.
ISSN: 0002-9513.
DOCUMENT TYPE: Article
LANGUAGE: English
AB We investigated the effects of catecholamines on acetylcholine (ACh) release from **equine** airway parasympathetic nerves. Trachealis strips were suspended in 2-ml tissue baths with Krebs-Henseleit solution containing atropine (10-7 M), neostigmine (10-6 M), and **guanethidine** (10-5 M). Electrical field stimulation (20 V, 0.5 ms, 0.5 Hz, for 15 min) was applied, and ACh was measured by high-performance liquid chromatography with electrochemical detection. Epinephrine (Epi) and norepinephrine (NE) inhibited ACh release in a concentration-dependent manner. Inhibition was attenuated by the alpha-2-adrenoceptor antagonist **idazoxan** (10-6 M) but not by the alpha-2-antagonist prazosin (10-6 M). After alpha-2-blockade with **idazoxan** (10-5 to 10-4 M), Epi but not NE augmented ACh release. Isoproterenol (10-7 to 10-5 M) increased ACh release, an effect that was reversed by the beta-2-adrenoceptor antagonist ICI-118,551 (10-5 M) but not by the beta-1-adrenoceptor antagonist atenolol (10-5 M). Our results indicate that **horse** airway cholinergic nerves are modulated by both alpha-2-inhibitory and beta-2-excitatory adrenoceptors, with the former being predominant.

L230 ANSWER 23 OF 51 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:118941 BIOSIS
DOCUMENT NUMBER: PREV199497131941
TITLE: Prejunctional alpha-2-adrenoceptors inhibits acetylcholine release from cholinergic nerves in **equine** airways.
AUTHOR(S): Yu, Mingfu; Wang, Zhaowan; Robinson, N. Edward (1)
CORPORATE SOURCE: (1) Dep. Large Anim. Clinical Sci., Mich. State Univ., East Lansing, MI 48824 USA
SOURCE: American Journal of Physiology, (1993) Vol. 265, No. 6 PART 1, pp. L565-L570.
ISSN: 0002-9513.
DOCUMENT TYPE: Article
LANGUAGE: English
AB To determine the presence and function of alpha-2-adrenoceptors on cholinergic nerves innervating **horse** airway smooth muscle, the effects of some alpha-2-adrenoceptor agents on contractions of and acetylcholine (ACh) release from **equine** airway smooth muscle preparations were studied. Muscle contractions were elicited by either electrical field stimulation (EFS) or exogenous ACh. ACh release was induced by EFS and measured by high-pressure liquid chromatography and electrochemical detection. The alpha-2-adrenoceptor agonists **clonidine** (10-7 to 10-5 M) and UK-14,304 (10-8 to 10-6 M) concentration dependently inhibited ACh release and the contractile response to EFS but not the response to exogenous ACh. This inhibition was attenuated by the- alpha-2-adrenoceptor antagonists **yohimbine** and **idazoxan** but not by the alpha-1-adrenoceptor antagonist prazosin. These results indicate that alpha-2-adrenoceptors exist on cholinergic nerves innervating **equine** airway smooth muscle, and activation of these receptors inhibits cholinergic neurotransmission. The observation that **yohimbine** alone had little effect on the

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contractile response to EFS suggests that, under these experimental conditions, endogenous norepinephrine had no influence on tracheal cholinergic neurotransmission via prejunctional alpha-2-adrenoceptors.

L230 ANSWER 24 OF 51 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1986:322971 BIOSIS
DOCUMENT NUMBER: BA82:47276
TITLE: POTENTIATION OF **CLONIDINE** ANALGESIA BY AMITRIPTYLINE.
AUTHOR(S): ADITHAN C; SIVAGNANAM G; SWAIN R; SHASHINDRAN C H; BAPNA J S
CORPORATE SOURCE: DEP. PHARMACOL., JAWAHARLAL INST. POSTGRADUATE MED. EDUCATION AND RES., PONDICHERRY 605 006, INDIA.
SOURCE: INDIAN J EXP BIOL, (1986) 24 (4), 256-258. CODEN: IJEBA6. ISSN: 0019-5189.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Effect of amitriptyline pretreatment on **clonidine** analgesia was assessed in mouse by acetic acid writhing assay. Amitriptyline potentiated **clonidine** analgesia and produced a parallel shift of the dose-response curve of the latter, suggesting a common pathway for their **analgesic** activity. Naloxone failed to **reverse** their **analgesic** activity, whereas **yohimbine**, a selective alpha-2 blocker, completely revesed it. It is suggested that their analgesic activity is not mediated through opioid receptors, but by alpha-2 adrenergic receptors.

L230 ANSWER 25 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:441782 CAPLUS
DOCUMENT NUMBER: 115:41782
TITLE: Analgesic mechanism of opioid analgesics at the spinal level. 2. Interaction of opiate and monoamine systems.
AUTHOR(S): Omote, Keiichi; Kitahata, Luke M.; Collins, J. G.
CORPORATE SOURCE: Dep. Anesthesiol., Sapporo Med. Coll., Sapporo, Japan
SOURCE: Sapporo Igaku Zasshi (1990), 59(5), 419-26 CODEN: SIZSAR; ISSN: 0036-472X
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB This study investigated the interaction between opiate receptor subtypes and monoamines (alpha 2 adrenergic agonist and serotonin) at the level of the spinal cord. Extracellular activity of a single wide dynamic range (WDR) neurons in the spinal dorsal horn which was evoked by radiant heat stimulus (51.degree.) was recorded in decerebrate, spinally transected **cats**. The first study examd. the synergism between an opiate and the alpha 2 adrenergic agonist clonidine, to identify the subtypes of the opiate that were likely to be involved in such synergistic suppression of noxiously evoked activity of a WDR neuron. Spinally administered ineffective dosage of morphine (25 .mu.g), DADL (delta/mu agonist, 20 .mu.g) and DPDPE (selective delta agonist, 30 .mu.g) combined with ineffective dosage of clonidine (5 .mu.g) produced a significant synergistic suppression of evoked WDR neuronal activity. However, ineffective and effective dosage of DAGO (selective mu agonist, 1 an 1.5 .mu.g, resp.) did not show any synergistic action with clonidine. The synergism between morphine and clonidine was reversed by the i.v. selective delta antagonist ICI174,864. In the second study, the synergism between morphine and serotonin was examd. Ineffective and effective dosage of serotonin (250 and 500 .mu.g, resp.) combined with an ineffective dosage of morphine produced only additive suppression, but not synergistic suppression. The third study investigated the existence of cross-antagonism between the opiate and monoamines systems. There was no cross-antagonism reactivity; neither naloxone nor ICI174,864 was able to reverse the suppression of clonidine or serotonin, and the alpha 2

adrenergic antagonist yohimbine was not able to reverse the suppression of opiates. These results indicate that opiates interact at the spinal delta receptors to produce a synergistic interaction of suppressing evoked WDR neuronal activity with spinal clonidine, but not serotonin. It also demonstrates that opiates and monamines act directly on the opiate and monoamine receptors, resp.

IT **146-48-5**, Yohimbine **4205-90-7**, Clonidine
RL: BIOL (Biological study)
(opioid system interaction with, at spinal level, analgesia in relation to)

L230 ANSWER 26 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1984:563609 CAPLUS
DOCUMENT NUMBER: 101:163609
TITLE: Effect of .alpha.2-adrenergic agents upon central etorphine antinociception in the **cat**
AUTHOR(S): Ossipov, Michael H.; Malseed, Roger T.; Eisenman, Leonard M.; Goldstein, Frederick J.
CORPORATE SOURCE: Dep. Pharmacol. Toxicol., Philadelphia Coll. Pharm. Sci., Philadelphia, PA, 19104, USA
SOURCE: Brain Res. (1984), 309(1), 135-42
CODEN: BRREAP; ISSN: 0006-8993
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Systemic (s.c.) administration of .alpha.2 agonists clonidine [**4205-90-7**] (25-100 .mu./kg) or guanfacine [**29110-47-2**] (50-400 .mu.g/kg) elicited antinociception as assessed by the **cat** tail-flick model and potentiated in a dose-dependent manner the antinociceptive effect of etorphine [14521-96-1] (2.5 .mu.g) administered directly into the periaqueductal gray. Conversely, systemic yohimbine [**146-48-5**] (1 mg/kg) attenuated the effects of central etorphine and diminished potentiation of etorphine by the .alpha.2-agonists. Prior microinjection of clonidine (5 .mu.g) or guanfacine (5 .mu.g) into the locus coeruleus (LC) reduced the intensity of central etorphine antinociception whereas central yohimbine (20 .mu.g) pretreatment increased peak antinociceptive activity and prolonged the duration of etorphine. Thus, systemic .alpha.2 agonists are inherently antinociceptive and potentiate central narcotic antinociception; however, the site of interaction between .alpha.-agonists and opiates does not appear to be the LC inasmuch as .alpha.2-agonists attenuate the antinociceptive effect of etorphine when administered directly into the LC. A spinal site of action is suggested.

IT **146-48-5 4205-90-7 29110-47-2**
RL: BIOL (Biological study)
(analgesia from etorphine response to)

L230 ANSWER 27 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1983:191307 CAPLUS
DOCUMENT NUMBER: 98:191307
TITLE: Interactions of drugs active at opiate receptors and drugs active at .alpha.2-receptors on various test systems
AUTHOR(S): Browning, S.; Lawrence, D.; Livingston, A.; Morris, B.
CORPORATE SOURCE: Dep. Pharmacol., Univ. Bristol Med. Sch., Bristol, BS8 1TD, UK
SOURCE: Br. J. Pharmacol. (1982), 77(3), 487-91
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The actions of the opiate receptor drugs, morphine [57-27-2], methionine-enkephalin [58569-55-4], and naloxone [465-65-6] were compared with the actions of the .alpha.2-receptor drugs, clonidine [**4205-90-7**], xylazine [7361-61-7] and yohimbine [**146-48-5**

] on analgesic tests, in vitro bioassay (guinea-**pig** ileum and mouse vas deferens), and radioligand displacement studies on rat brain membrane prepns. Thus drugs which act on .alpha.2-receptors interfere with the in vivo analgesic effects of opiates and weakly displace opioid radioligand binding, but opioids do not affect .alpha.2-agonist analgesia and do not appear to displace .alpha.2-agonist radioligand binding.

IT **146-48-5 4205-90-7**
RL: BIOL (Biological study)
(opiate receptor agonists interaction with)

L230 ANSWER 28 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96314304 EMBASE
DOCUMENT NUMBER: 1996314304
TITLE: Effects of clonidine, yohimbine and idazoxan on isolated carotid arteries of dog.
AUTHOR: Gintautas J.; Abadir A.R.; Kwalburn M.; Mayda J. II; Kraynack B.J.
CORPORATE SOURCE: Brookdale Hospital Medical Center,Brooklyn, NY 11212, United States
SOURCE: Proceedings of the Western Pharmacology Society, (1996) 39/- (45-46).
ISSN: 0083-8969 CODEN: PWPSA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

L230 ANSWER 29 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94023495 EMBASE
DOCUMENT NUMBER: 1994023495
TITLE: The rostroventromedial medulla is not involved in .alpha.2-adrenoceptor-mediated antinociception in the rat.
AUTHOR: Hamalainen M.M.; Pertovaara A.
CORPORATE SOURCE: Department of Physiology, University of Helsinki, P.O. Box 9,00014 Helsinki, Finland
SOURCE: Neuropharmacology, (1993) 32/12 (1411-1418).
ISSN: 0028-3908 CODEN: NEPHBW
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 001 Anatomy, Anthropology, Embryology and Histology
002 Physiology
008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The aim of the current study was to investigate the role of the rostroventromedial medulla (RVM) in .alpha.2-adrenoceptor-mediated antinociception. Medetomidine or clonidine, selective .alpha.2-adrenoceptor agonists were microinjected into the RVM in unanesthetized rats with a chronic guide cannula. The antinociceptive effects were evaluated using the tail-flick and hot-plate tests. For comparison, medetomidine was microinjected into the cerebellum or the periaqueductal gray (PAG). To study the role of medullospinal pathways, the tail-flick latencies were also measured in spinalized rats. The reversal of the antinociception induced by intracerebral microinjections of medetomidine was attempted by s.c. atipamezole, a selective .alpha.2-adrenoceptor antagonist. The reversal of the antinociception induced by systemic administration of medetomidine was attempted by microinjections of 5% lidocaine or atipamezole into the RVM. When administered into the RVM, medetomidine produced a dose-dependent (1-30 .mu.g) antinociception in the tail-flick and hot-plate tests, which antinociceptive effect was

completely reversed by atipamezole (1 mg/kg, s.c.). Also clonidine produced a dose-dependent (3-30 .mu.g) antinociception following microinjection into the RVM. Microinjections of medetomidine into the cerebellum or the PAG produced an identical dose-response curve in the tail-flick test as that obtained following microinjection into the RVM. In spinalized rats the antinociceptive effect (tail-flick test) induced by medetomidine microinjected into the RVM was not less effective than in intact rats. Lidocaine (5%) or atipamezole (5 .mu.g) microinjected into the RVM did not attenuate the antinociception induced by systemically administered medetomidine (100 .mu.g/kg, s.c.). The adapting skin temperature of the tail was increased in a nonmonotonic fashion following medetomidine. The results indicate that the RVM is not a site which is critical for the .alpha.2-adrenergic antinociception. The antinociception following intracerebral microinjections of medetomidine into the RVM, PAG or the cerebellum in the current study can be explained by a spread of the .alpha.2-adrenoceptor agonist into the spinal level to activate directly spinal .alpha.2-adrenoceptors. Also, the antinociception following systemic administration of medetomidine can be explained by spinal .alpha.2-adrenergic mechanisms. The medetomidine-induced increase of the adapting skin temperature may have attenuated the medetomidine-induced increases in the response latencies to noxious heat.

L230 ANSWER 30 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93202270 EMBASE
DOCUMENT NUMBER: 1993202270
TITLE: Analgesic effect of morphine, clonidine and serotonin microinjected into the PTN of rats.
AUTHOR: Kumar A.; Raghubir R.; Dhawan B.N.
CORPORATE SOURCE: Division of Pharmacology, Central Drug Research Institute,Lucknow 226001, India
SOURCE: NeuroReport, (1993) 4/7 (944-946).
ISSN: 0959-4965 CODEN: NERPEZ
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The study was aimed to delineate the neurotransmitter receptors involved in pretectal analgesic mechanisms by direct microinjection of neurotransmitter agonists and antagonists through chronically implanted cannulae in the pretectal nucleus of rats. Morphine, clonidine and serotonin, at doses of 2.5 and 5.0 .mu.g microinjected into the pretectal nucleus, produced a significant and prolonged analgesia as measured by the tail-flick test. The analgesia produced by morphine, clonidine and serotonin is significantly attenuated by pretreatment of the animals with naloxone (1 .mu.g), yohimbine (5 .mu.g) and methysergide (5-10 .mu.g) respectively. The results indicate the possible involvement of opioid, adrenergic and serotonergic mechanisms in pretectal analgesia.

L230 ANSWER 31 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93174015 EMBASE
DOCUMENT NUMBER: 1993174015
TITLE: Involvement of .alpha.2-receptors in the analgesia induced by transient forebrain ischemia in rats.
AUTHOR: Merlo Pich E.; Grimaldi R.; Zini I.; Frasoldati A.; Marrama P.; Agnati L.F.
CORPORATE SOURCE: Institute of Human Physiology, University of Modena, Via Campi 287,41100 Modena, Italy
SOURCE: Pharmacology Biochemistry and Behavior, (1993) 45/3 (607-614).
ISSN: 0091-3057 CODEN: PBBHAU

[redacted]

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Transient forebrain ischemia induced in rats by the four-vessel occlusion method produced analgesic effects in the hotplate test that persisted for 2 weeks. Ischemia-induced analgesia was attenuated by low doses of .alpha.2-agonist clonidine (0.01-0.10 mg/kg, IP) and enhanced by low doses of .alpha.2-antagonists yohimbine (1-2 mg/kg, IP) and idazoxan (0.25-1.00 mg/kg, IP) administration 7 days after ischemia. Ischemia-induced analgesia was not affected by methysergide, naloxone, propranolol, or phenoxybenzamine administered 7 days after ischemia, when motor control and arousal level of rats recovered to normal conditions. The enhanced response to yohimbine was antagonized by pretreatment with clonidine (0.75 mg/kg, IP) and naloxone (10 mg/kg, IP), suggesting the involvement of endogenous opioid peptides. The enhanced response to yohimbine was still present 2 months after ischemia, when preischemic hotplate threshold was restored. As .alpha.2-agonists reduce and .alpha.2-antagonists increase the outflow of central noradrenaline, it is suggested that activation of central noradrenergic systems is involved in the mediation of ischemia-induced analgesia.

L230 ANSWER 32 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93040587 EMBASE
DOCUMENT NUMBER: 1993040587
TITLE: Naloxone potentiation of novelty-induced hypoalgesia: Characterization of the .alpha.-noradrenergic receptor subtype.
AUTHOR: Rochford J.; Dawes P.; Stewart J.
CORPORATE SOURCE: Ctr. Studies in Behav. Neurobiology, Department of Psychology, Concordia University,Montreal, Que., Canada
SOURCE: Pharmacology Biochemistry and Behavior, (1993) 44/2 (381-386).
ISSN: 0091-3057 CODEN: PBBHAU
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Repeated daily administration of the opiate receptor antagonist naloxone (10 mg/kg) attenuates the habituation of novelty-induced hypoalgesia. This effect can be reversed by the .alpha.2-noradrenergic receptor agonist clonidine and enhanced by the .alpha.2-antagonist yohimbine. The present experiments were conducted to provide further support for the importance of the .alpha.2-receptor and determine the possible influence of the .alpha.1-receptor. Naloxone's effect on novelty-induced hypoalgesia was not affected by pretreatment with the specific .alpha.1-receptor antagonist prazosin (0.2-1.0 mg/kg, SC) or the nonselective alpha antagonist phentolamine (2.0-10.0 mg/kg). In a second series of experiments, it was found that the potentiation of naloxone's effect by yohimbine (2 mg/kg) was reversed by clonidine (0.1 mg/kg) but was not influenced by prazosin or phentolamine. These results suggest that the .alpha.1-noradrenergic receptor subtype does not mediate the effect of naloxone on novelty-induced hypoalgesia. They also reinforce the importance of the .alpha.2-receptor subtype in the mediation of this

effect.

L230 ANSWER 33 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93283330 EMBASE
DOCUMENT NUMBER: 1993283330
TITLE: Effect of naloxone on the habituation of novelty-induced hypoalgesia: The collateral inhibition hypothesis revisited.
AUTHOR: Rochford J.; Dawes P.
CORPORATE SOURCE: Douglas Hospital Research Center, Department of Psychiatry, McGill University, 6875 Boulevard LaSalle,Verdun, Que. H4H 1R3, Canada
SOURCE: Pharmacology Biochemistry and Behavior, (1993) 46/1 (117-123).
ISSN: 0091-3057 CODEN: PBBHAU
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Repeated daily administration of the opiate receptor antagonist naloxone prior to hotplate tests provokes longer paw-lick latencies by attenuating the habituation of novelty-induced hypoalgesia. This hypoalgesia has been found to persist when pain tests are subsequently conducted following saline administration. The present experiments were conducted to determine whether the substrates mediating the hypoalgesia observed during naloxone and saline tests are similar or distinct. Neither the hypoalgesia observed during naloxone nor saline tests were affected by the induction of tolerance to the hypoalgesic effect of morphine, suggesting that both effects are mediated by nonopioid antinociceptive mechanisms. Previous work from our laboratory demonstrated that the hypoalgesia observed during naloxone tests is inhibited by clonidine, enhanced by yohimbine, and unaffected by prazosin and phentolamine. In the present article, we report a similar pattern of results for the hypoalgesia observed during saline tests. It is concluded that the substrates mediating both effects are similar. The results are discussed in relation to the possibility that an opioid substrate involved in habituative learning may be inhibitory on a nonopioid antinociceptive substrate.

L230 ANSWER 34 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92164684 EMBASE
DOCUMENT NUMBER: 1992164684
TITLE: Clonidine and yohimbine modulate the effects of naloxone on novelty-induced hypoalgesia.
AUTHOR: Rochford J.; Dawes P.
CORPORATE SOURCE: Douglas Hospital Research Center, 6875 Boulevard LaSalle,Verdun, Que. H4H 1R3, Canada
SOURCE: Psychopharmacology, (1992) 107/4 (575-580).
ISSN: 0033-3158 CODEN: PSCHDL
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Previous research has shown that repeated daily pretreatment with the opiate receptor blocker naloxone retards the development of habituation to novelty-induced hypoalgesia. The present experiments were conducted in order to determine whether noradrenergic substrates mediate this effect.

[redacted]

Animals in the NAL condition were administered 10 mg/kg naloxone prior to assessment of pain sensitivity on a 48.5.degree.C hot plate. Control animals (SAL condition) were administered saline prior to pain assessment, and naloxone 2-4 h later. Paw lick latencies declined over repeated tests in SAL animals, suggesting the habituation of novelty hypoalgesia. Naloxone pretreatment attenuated this decline. The longer paw lick latencies observed in NAL condition animals were reduced by administration of 2 .mu.g/kg clonidine, a specific noradrenergic alpha-2 receptor agonist, and enhanced in a dose dependent (0.5-4.0 mg/kg) fashion by the alpha-2 antagonist yohimbine. Clonidine and yohimbine either failed to alter pain reactivity in control animals, or produced less marked effects than those observed in naloxone-exposed animals. These results suggest that noradrenergic substrates mediate naloxone's effects on novelty hypoalgesia.

L230 ANSWER 35 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92276784 EMBASE
DOCUMENT NUMBER: 1992276784
TITLE: Spinal 5-HT pathways and the antinociception induced by intramedullary clonidine in rats.
AUTHOR: Lin M.-T.; Su C.F.
CORPORATE SOURCE: Department of Physiology, National Cheng Kung University, Medical College,Tainan City, Taiwan,Province of China
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology, (1992) 346/3 (333-338).
ISSN: 0028-1298 CODEN: NSAPCC
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 001 Anatomy, Anthropology, Embryology and Histology
002 Physiology
008 Neurology and Neurosurgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The possible involvement of spinal 5-hydroxytryptamine (5-HT) pathways in antinociception induced by microinjection of clonidine into the ventrolateral surface of the medulla oblongata was investigated in rats. Microinjection of clonidine (10-20 .mu.g), but not yohimbine (1 .mu.g) or 0.9% saline, into the lateral medulla prolonged the hot plate latency in rats. This clonidine-induced antinociception was abolished by intramedullary injection of the alpha2-adrenoceptor antagonist, yohimbine. Selective destruction of spinal 5-HT neurons produced by intraspinal injection of 5,7-dihydroxytryptamine (5,7-DHT; 10 .mu.g) or postsynaptic blockade of spinal 5-HT receptors produced by intrathecal injection of cyproheptadine (1 .mu.g; a mixed 5-HT1/5-HT2 antagonist) also abolished clonidine-induced antinociception. Rats given 5,7-DHT intraspinally or cyproheptadine intrathecally showed a decrease in hot plate latency as compared with the controls. In anesthetized rats, the 5-HT release from the thoracic spinal cord was enhanced by microinjection of clonidine into the lateral medulla. This enhanced spinal 5-HT release evoked by intramedullary injection of clonidine was abolished by pretreatment of rats with intraspinal injection of 5,7-DHT. These results indicate that 5-HT pathways to the spinal cord mediate the antinociceptive effect induced by microinjection of clonidine into the ventrolateral surface of the medulla oblongata in rats.

L230 ANSWER 36 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 91233662 EMBASE
DOCUMENT NUMBER: 1991233662
TITLE: Participation of an .alpha.2-mediated mechanism in the production of forced swimming-stress induced analgesia in

mice.
AUTHOR: Tokuyama S.; Takahashi M.; Kaneto H.
CORPORATE SOURCE: Department of Pharmacology, Faculty of Pharmaceutical Sciences, Nagasaki University, Bunkyo-machi, Nagasaki 852, Japan
SOURCE: Journal of Pharmacobio-Dynamics, (1991) 14/6 (357-361). ISSN: 0386-846X CODEN: JOPHDQ
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB In mice, both swimming-stress induced analgesia (SW-SIA) and clonidine (CLO) analgesia were dose dependently antagonized by yohimbine, an .alpha.2-adrenoceptor antagonist, but not by naloxone, an opioid .mu.-antagonist, SW-SIA was potentiated by subanalgesic dose of CLO, and CLO analgesia was enhanced by SW-SIA. Animals tolerant to CLO analgesia were tolerant to SW-SIA, in contrast, CLO analgesia was potentiated in SW-SIA tolerant mice. Thus, SW-SIA and CLO analgesia partially share a common .alpha.2-adrenergic-dependent mechanism, for their production.

L230 ANSWER 37 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 89117389 EMBASE
DOCUMENT NUMBER: 1989117389
TITLE: Noradrenergic and opioidergic influences on the antinociceptive effect of clomipramine in the formalin test in rats.
AUTHOR: Ansuategui M.; Naharro L.; Feria M.
CORPORATE SOURCE: Department of Pharmacology, Faculty of Medicine, University of La Laguna, Tenerife, Spain
SOURCE: Psychopharmacology, (1989) 98/1 (93-96). ISSN: 0033-3158 CODEN: PSCHDL
COUNTRY: Germany
DOCUMENT TYPE: Journal
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Although tricyclic antidepressants are especially useful in the treatment of chronic pain conditions, most of the work about its mechanism of action has been made on acute pain tests. The present study was aimed at studying the role played by noradrenergic and opioidergic influences on the antinociceptive activity of subchronically administered clomipramine in the formalin test (a tonic pain model) in rats. Clomipramine produced antinociception after 7 days, administration (2.5 mg/kg/day), an effect equivalent to that obtained by acute morphine (5 mg/kg). The antinociceptive effect of clomipramine was inhibited by the following: nonspecific blocking of alpha1- and alpha2-adrenoceptors by phentolamine, specific blocking of alpha1-adrenoceptors by prazosin; stimulation of alpha2 receptors by clonidine; and blocking of the opioid receptors by naloxone. Blocking the alpha2-receptors with yohimbine did not antagonize the effect of clomipramine. These results suggest that clomipramine produces antinociception in this test, partly via the participation of the endogenous opioid system and partly by further activating or potentiating previously activated noradrenergic pathways which are involved in the control of pain information.

L230 ANSWER 38 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 89023410 EMBASE
DOCUMENT NUMBER: 1989023410
TITLE: Different alpha-receptor subtypes are involved in clonidine-produced analgesia in different pain tests.

AUTHOR: Tasker R.A.R.; Melzack R.
CORPORATE SOURCE: Department of Psychology, McGill University, Montreal, Que. H3A 1B1, Canada
SOURCE: Life Sciences, (1989) 44/1 (9-17).
ISSN: 0024-3205 CODEN: LIFSAK
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Dose-response curves for clonidine-produced analgesia in rats were constructed using the tail-flick and formalin tests. Subsequently, the relative role of alpha1 and alpha2 receptors in clonidine analgesia in each of these tests was determined using systemic administration of vehicle controls, tolazoline, yohimbine and prazosin prior to injection of an ED50 dose of clonidine. Clonidine was found to be significantly more potent in the formalin test than in the tail-flick test. Furthermore, clonidine analgesia in the tail-flick test was completely antagonized by tolazoline and yohimbine, but not by prazosin, whereas clonidine was antagonized by prazosin, whereas clonidine was antagonized by tolazoline and prazosin, but not by yohimbine in the formalin test. The implications of these findings with regard to the contributions of different alpha-receptor subtypes to clonidine-produced analgesia in different pain tests are discussed.

L230 ANSWER 39 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 88052365 EMBASE
DOCUMENT NUMBER: 1988052365
TITLE: Analgesic effects intrathecally-applied .alpha.2-adrenoceptor agonists in conscious, unrestrained sheep.
AUTHOR: Waterman A.; Livingston A.; Bouchenafa O.
CORPORATE SOURCE: Dept Veterinary Surgery, University of Bristol, BS8 1TD, United Kingdom
SOURCE: Neuropharmacology, (1988) 27/2 (213-216).
ISSN: 0028-3908 CODEN: NEPHBW
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Intrathecal injections of small volumes of the .alpha.2-adrenoceptor agonists, xylazine and clonidine, into the cervical region of the spinal cord of conscious unrestrained sheep produced a dose-dependent analgesia of the forelimbs as measured using a mechanical pressure device. Intravenous injection of the .alpha.2-adrenoceptor antagonist, idazoxan completely abolished the analgesic effects of the intrathecally applied .alpha.2-adrenoceptor agonists. Subsequent studies using [3H] clonidine injected at a similar dose and volume via the intrathecal catheters, indicated that the volume of drug used, 100 .mu.l, gave a localisation of the drug limited to about five vertebral segments around the catheter tip.

L230 ANSWER 40 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 86247048 EMBASE
DOCUMENT NUMBER: 1986247048
TITLE: Dissociation of locomotor impairment from mydriasis evoked by clonidine injected into cat's rostral hypothalamus.
AUTHOR: Beleslin D.B.; Rezvani A.H.; Myers R.D.
CORPORATE SOURCE: Department of Psychiatry, University of North Carolina School of Medicine, Chapel Hill, NC 27514, United States

SOURCE: Brain Research Bulletin, (1986) 17/3 (379-385).
CODEN: BRBUDU
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
002 Physiology
008 Neurology and Neurosurgery
012 Ophthalmology
LANGUAGE: English

L230 ANSWER 41 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 86047886 EMBASE
DOCUMENT NUMBER: 1986047886
TITLE: .alpha.2-Adrenoceptor antagonists as antidepressants.
AUTHOR: Pinder R.M.
CORPORATE SOURCE: Scientific Development Group, Organon International, 5340 BH Oss, Netherlands
SOURCE: Drugs of the Future, (1985) 10/10 (841-857).
CODEN: DRFUD4
COUNTRY: Spain
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: English

L230 ANSWER 42 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 82150314 EMBASE
DOCUMENT NUMBER: 1982150314
TITLE: Modulation of central etorphine analgesia by alpha-2 agonists in the cat.
AUTHOR: Ossipov M.H.; Goldstein F.J.; Malseed R.T.
CORPORATE SOURCE: Dept. Pharmacol. Toxicol., Coll. Pharm. Sci., Philadelphia, PA 19104, United States
SOURCE: Federation Proceedings, (1982) 41/4 (No. 6104).
CODEN: FEPRA7
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: English

L230 ANSWER 43 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 82216170 EMBASE
DOCUMENT NUMBER: 1982216170
TITLE: [Tolazoline as an antagonist of xylazine-induced sedation in the ewe].
LA TOLAZOLINE COMME ANTAGONISTE DE LA SEDATION PAR LA XYLAZINE CHEZ LE MOUTON.
AUTHOR: Zingoni M.R.; Garcia-Villar R.; Toutain P.L.
CORPORATE SOURCE: Stn. Pharmacol. Toxicol., Inst. Natl. Rech. Agron., F-31300 Toulouse, France
SOURCE: Revue de Medecine Veterinaire, (1982) 133/5 (335-339).
CODEN: RVMVAH
COUNTRY: France
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: French
SUMMARY LANGUAGE: English; German

L230 ANSWER 44 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 83012726 EMBASE
DOCUMENT NUMBER: 1983012726
TITLE: Selective stimulation of dopamine and noradrenaline autoreceptors by B-HT 920 and B-HT 933, respectively.
AUTHOR: Anden N.E.; Golembiowska-Nikitin K.; Thornstrom U.

CORPORATE SOURCE: Dep. Med. Pharmacol., Biomedicum, S-751 23 Uppsala, Sweden
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology, (1982) 321/2 (100-104).
CODEN: NSAPCC
COUNTRY: Germany
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
LANGUAGE: English

AB The azepine derivatives B-HT 920 and B-HT 933 did not increase the motor activity of mice pretreated with reserpine or reserpine plus apomorphine, indicating that they do not stimulate postsynaptic dopamine receptors or noradrenaline .alpha.1-receptors in the brain. The motor activity of mice not pretreated with reserpine was reduced by a low dose of B-HT 920 and by B-HT*933. The .alpha.2-adrenoreceptor antagonist yohimbine **reversed** the **sedation** induced by B-HT 933, but not that induced by B-HT 920. B-HT 933 and a high dose of B-HT 920 retarded the .alpha.-methyltyrosine-induced disappearance of noradrenaline in the mouse brain by a yohimbine-sensitive mechanism. The .alpha.-methyltyrosine-induced disappearance of dopamine in the mouse brain was decelerated by a low dose of B-HT 920 and to a smaller degree by B-HT 933. The effects were inhibited by the dopamine receptor antagonist haloperidol. The effect of B-HT 933, but not that of B-HT 920, was partly antagonized by yohimbine. The enhanced synthesis of dopamine in the corpus striatum of mice following treatment with gammabutyrolactone was completely antagonized by B-HT 920, but not by B-HT 933, via a haloperidol-sensitive mechanism. The synthesis of noradrenaline in the brain stem and in the hemispheres was reduced by B-HT 933 via a yohimbine-sensitive mechanism. The results indicate that B-HT 920 can selectively and potently stimulate dopamine autoreceptors and that B-HT 933 can preferentially stimulate noradrenaline autoreceptors (.alpha.2-adrenoreceptors). These actions might cause the decreases in motor activity observed in mice not pretreated with reserpine.

L230 ANSWER 45 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 81124024 EMBASE
DOCUMENT NUMBER: 1981124024
TITLE: Characterization of .alpha.-adrenoceptors participating in the central hypotensive and sedative effects of clonidine using yohimbine, rauwolscine and corynanthine.
AUTHOR: Timmermans P.B.M.W.M.; Schoop A.M.C.; Kwa H.Y.; Van Zwieten P.A.
CORPORATE SOURCE: Div. Pharmacother., Dept. Pharm., Univ., 1018 TV Amsterdam, Netherlands
SOURCE: European Journal of Pharmacology, (1981) 70/1 (7-15).
CODEN: EJPHAZ
COUNTRY: Netherlands
DOCUMENT TYPE: Journal
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

AB The central .alpha.-adrenoceptors responsible for mediating the clonidine-induced central hypotension in anaesthetized cats and sedation in mice have been characterized according to their sensitivities to the .alpha.-adrenoceptor antagonist yohimbine and its two diastereomeric congeners rauwolscine and corynanthine. Yohimbine and rauwolscine (1-10 .mu.g/kg) dose-dependently antagonized the central hypotensive response to clonidine (1 .mu.g/kg) applied 15 min later. Greater amounts of corynanthine (30-100 .mu.g/kg) had to be administered to diminish the central depressor effect of clinidine. In these studies the drugs were infused via the left vertebral artery. The prolongation of the hexobarbitone-induced loss of the righting reflex in mice by clonidine (0.3 mg/kg, i.p.) was inhibited by previous treatment with yohimbine and

rauwolscine (0.04-5 mg/kg, i.p.) in a dose-dependent manner, but not by corynanthine. Binding experiments with rat isolated cerebral membranes demonstrated the higher affinity of yohimbine and rauwolscine for the [3H]prazosin-specific binding sites. The reverse was found for corynanthine. The relative potencies of yohimbine, rauwolscine and corynanthine in inhibiting these central effects of clonidine are comparable to their order of efficacies in blocking peripheral .alpha.2-adrenoceptors. Accordingly, clonidine-induced central hypotension and sedation are mediated by .alpha.2-adrenoceptors.

L230 ANSWER 46 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 80216474 EMBASE
DOCUMENT NUMBER: 1980216474
TITLE: Sedative and analgesic actions of methoxylated 2-aminotetralins; Involvement of .alpha.1- and .alpha.2-adrenoreceptors.
AUTHOR: Rusterholz D.B.; Dryer S.E.; Long J.P.; et al.
CORPORATE SOURCE: Dept. Pharmacol., Coll. Med., Univ. Iowa, Iowa City, Ia. 52242, United States
SOURCE: European Journal of Pharmacology, (1980) 65/2-3 (201-211). CODEN: EJPHAZ
COUNTRY: Netherlands
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
024 Anesthesiology
LANGUAGE: English
AB Three 5,8-dimethoxylated derivatives of 2-aminotetralin (2-AT) were compared with clonidine, methoxamine and phenylephrine in tests for sedation (inhibition of exploratory activity) and analgesia. In both tests the 2-AT derivatives were less potent than clonidine, but more potent than methoxamine or phenylephrine. Antagonism of the 2-AT derivative, DR-31, and clonidine by yohimbine in both tests argues for the involvement of .alpha.1-adrenoreceptors in the mediation of these behavioral effects. .alpha.1-Adrenoreceptors may also mediate an inhibition of exploratory activity since the inhibition induced by methoxamine was antagonized by phenoxybenzamine (POB) but not by yohimbine. The methoxylated 2-AT derivatives, which have previously been shown to exert potent peripheral .alpha.1-agonism are now demonstrated to have sedative and analgesic effects characteristic of central .alpha.2-adrenergic stimulation.

L230 ANSWER 47 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 76177173 EMBASE
DOCUMENT NUMBER: 1976177173
TITLE: A study of the central effects of sympathomimetic drugs: EEG and behavioural investigations on clonidine and naphazoline.
AUTHOR: Florio V.; Bianchi L.; Longo V.G.
CORPORATE SOURCE: Ist. Sup. San., Rome, Italy
SOURCE: Neuropharmacology, (1975) 14/10 (707-714). CODEN: NEPHBW
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
008 Neurology and Neurosurgery
050 Epilepsy
LANGUAGE: English
AB The effect of clonidine and naphazoline on the EEG and behaviour of rats, rabbits and cats, and the modifications of these effects by .alpha. adrenolytic drugs and other compounds acting on the sympathetic system, have been studied. Clonidine and naphazoline induced behavioural depression and EEG synchronization in all animal species studied. These effects were prevented by the administration of tolazoline, phentolamine

and yohimbine, but not by phenoxybenzamine. Pretreatment with .alpha. methyl p tyrosine was only partially effective in preventing the EEG synchronization due to clonidine. Reserpine was without effect. Amphetamine proved able to reverse the effects of clonidine and furthermore, clonidine attenuated the behavioural and EEG changes due to amphetamine. These data suggest that clonidine and naphazoline induce sedation and EEG synchronization through stimulation of the central .alpha. adrenergic receptors.

L230 ANSWER 48 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 74208439 EMBASE
DOCUMENT NUMBER: 1974208439
TITLE: [Sedative effects of clonidine and antagonism by .alpha. adrenoreceptor blocking agents on EEG and behavior in rabbits and cats].
ANTAGONISME DE L'ACTION SEDATIVE DE LA CLONIDINE PAR QUELQUES .alpha. ADRENOLYTIQUES: ETUDE ELECTROCORTICOGRAPHIQUE ET COMPORTEMENTALE CHEZ LE LAPIN ET LA CHAT.
AUTHOR: Tran Quang Loc; Tsoucaris Kupfer D.; Bogaievsky Y.; et al.
CORPORATE SOURCE: Dept. Pharmacol., Fac. Med. Paris Broussais, Hotel Dieu, Paris, France
SOURCE: Journal de Pharmacologie, (1974) 5/1 (51-62).
CODEN: JNPHAG
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
008 Neurology and Neurosurgery
LANGUAGE: French
AB Clonidine (0.1-0.5 mg/kg) and xylazine (1-2 mg/kg) induced high slow waves in rabbits and cats with chronically implanted electrodes. Piperoxan (2-4 mg/kg) and yohimbine (1-2 mg/kg) effectively antagonized these effects. Tolazoline (4 mg/kg) was less effective. In contrast, phentolamine (20 mg/kg) and azapetine (10 mg/kg) were ineffective. Dibenamine (10 mg/kg) and to a lesser degree, phenoxybenzamine (5-10 mg/kg) reversed the recording of high slow waves in arousal, but did not change the behavioral sedation. These experiments suggest that clonidine and xylazine induced electroencephalographic changes by activating central .alpha. adrenoceptors related to but distinct from the peripheral .alpha. adrenoceptors and from the adrenoceptors involved in behavioral sedation.

L230 ANSWER 49 OF 51 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-686985 [67] WPIDS
DOC. NO. CPI: C2000-208924
TITLE: Use of I1 imidazoline receptor agonist for preventing, treating or diagnosing cardiovascular complications in patients with obstructive sleep apnea.
DERWENT CLASS: B02 B03
INVENTOR(S): GROTE, L; HEDNER, J
PATENT ASSIGNEE(S): (GROT-I) GROTE L; (HEDN-I) HEDNER J
COUNTRY COUNT: 92
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000061144	A1	20001019	(200067)*	EN	16

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000043229 A 20001114 (200108)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000061144	A1	WO 2000-SE688	20000411
AU 2000043229	A	AU 2000-43229	20000411

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000043229	A	Based on	WO 200061144

PRIORITY APPLN. INFO: SE 1999-1295 19990413

AB WO 200061144 A UPAB: 20001223
NOVELTY - The inhibition of activation of the sympathoadrenergic system, by administration of I1 imidazoline receptor agonists, can be used to prevent or treat cardiovascular complications in patients with obstructive sleep apnea.

DETAILED DESCRIPTION - A method of treating and/or preventing sympathetically induced cardiovascular complications selected from coronary artery disease, cardiac failure, myocardial infarction and stroke, in patients with obstructive sleep apnea disorder, comprises inhibiting activation of the sympathoadrenergic system by administration of an I1 imidazoline receptor agonist (IRA) prior to and/or during a period of sleep.

An INDEPENDENT CLAIM is included for use of an IRA in a diagnostic device, kit or composition for determination of sympathoadrenergic activation during sleep.

ACTIVITY - Cardiant. A double-blind, placebo controlled cross-over study of moxonidine was carried out in 3 patients with moderate OSA and 3 controls without OSA. One of the patients and 1 of the controls had systemic hypertension. Moxonidine (0.4 mg) or placebo was administered as a single evening dose. A wash out period of 1 week was applied between the 2 study nights. Resting awake plasma noradrenaline was reduced from 410, 405 and 387 pg/ml respectively after placebo to 212, 251 and 190 pg/ml after moxonidine administration in patients, and from 331, 312 and 285 pg/ml to 200, 165 and 202 pg/ml in controls. In treated patients, mean urinary methoxy catecholamine levels at night-time were reduced from 3.0 plus or minus 0.2 to 1.2 plus or minus 0.2 mmol/mol creatinine, and daytime excretion from 2.9 plus or minus 0.3 to 1.4 plus or minus 0.1 mmol/mol creatinine. Corresponding values for controls were 1.8 plus or minus 0.3 to 1.4 plus or minus 0.3 mmol/mol creatinine at night-time and 2.6 plus or minus 0.5 to 2.2 mmol/mol creatinine daytime. Mean blood pressure elevation during a 20 second apnea was 6.2 plus or minus 4.6 mmHg after moxonidine compared to 31.4 plus or minus 12.2 mmHg after placebo.

MECHANISM OF ACTION - None given.

USE - The method is useful for preventing, treating or diagnosing cardiovascular complications in patients with obstructive sleep apnea (OSA).

Dwg.0/0

L230 ANSWER 50 OF 51 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-337678 [28] WPIDS
DOC. NO. NON-CPI: N1999-253074
DOC. NO. CPI: C1999-099282
TITLE: New receptor with affinity for oxazoline type compounds.
DERWENT CLASS: B03 B04 D16 S03
INVENTOR(S): CONWAY, E L; GUNDLACH, A L; IAKOVIDIS, D; JACKMAN, G P; KING, P R; LOUIS, S N S; LOUIS, W J; NERO, T
PATENT ASSIGNEE(S): (UYME) UNIV MELBOURNE
COUNTRY COUNT: 84

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9924411	A1	19990520	(199928)*	EN	65
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW					
AU 9910127	A	19990531	(199941)		
EP 1044194	A1	20001018	(200053)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9924411	A1	WO 1998-AU919	19981105
AU 9910127	A	AU 1999-10127	19981105
EP 1044194	A1	EP 1998-952426	19981105
		WO 1998-AU919	19981105

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9910127	A	Based on	WO 9924411
EP 1044194	A1	Based on	WO 9924411

PRIORITY APPLN. INFO: AU 1997-202 19971105

AB WO 9924411 A UPAB: 19990719

NOVELTY - N-containing heterocycles of formula (I) which have selectivity for new Oxazoline (Ox) receptors over one or both of the alpha 2-adrenoreceptor and Imidazoline2 (I2) receptors of greater than 1 are new.

DETAILED DESCRIPTION - Compounds of formula (I) are new:

R = the residue of an organic compound;

X = O or S;

Y = a divalent group making up a 5 or 6 membered ring.

Compounds (I) have a selectivity for an Ox receptor over one or both of the alpha 2 and I2 receptors.

INDEPENDENT CLAIMS are included for the following:

(1) an isolated Ox receptor in sequencably pure form characterized by a high binding affinity for O501 and a poor binding affinity for methoxyidazoxan, **clonidine** and **idazoxan**;

(2) an isolated nucleic acid molecule which encodes an Ox receptor;

(3) a recombinant plasmid, cosmid, bacteriophage or other recombinant molecule comprising the nucleic acid molecule;

(4) a method for identifying a modulator or Ox receptor activity which comprises assaying recombinant Ox receptor activity in the presence of a potential modulator and comparing the activity to the activity of recombinant Ox receptor in the absence of the potential modulator.

ACTIVITY - Nootropic; Cerebroprotective; Neuroprotective; Antiparkinsonian; Ophthalmalogical; Antiulcer; Cardiant.

MECHANISM OF ACTION - Modulation of the Oxazoline (Ox) receptor with selectivity over one or both of the alpha 2-adrenoreceptor and Imidazoline2 (I2) receptors of greater than 1, preferably greater than 5.

USE - Compounds (I) Can be used to treat diseases of the CNS including dementia, mood disturbances, degenerative conditions, such as stroke and aging, ischemia, CNS trauma and neurodegenerative diseases e.g. Alzheimer's disease and Parkinson's disease, diseases of the

cardiovascular system e.g. hypertension and ischemic heart disease, diseases of the kidney including diseases which affect renal tubular function, diseases associated with abnormal adrenal gland secretions including hypertension, heart failure and oedema, hyperglycaemia, glaucoma, peptic ulcer and as analgesics.
Dwg.0/0

L230 ANSWER 51 OF 51 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1991-222666 [30] WPIDS
DOC. NO. CPI: C1991-096689
TITLE: Medicament for treatment of heart failure - comprises combination of alpha-2-adrenergic agonist and natriuretic peptide.
DERWENT CLASS: B05
INVENTOR(S): FENG, Q; HEDNER, T
PATENT ASSIGNEE(S): (FENG-I) FENG Q; (HEDN-I) HEDNER T; (QING-N) QINGPINGFENG; (THOM-N) THOMASHEDNER
COUNTRY COUNT: 14
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9109627	A	19910711	(199130)*	EN	15
RW: AT BE CH DE DK ES FR GB GR IT LU NL SE					
W: CA FI JP NO US					
SE 8904407	A	19910630	(199134)		
EP 510052	A1	19921028	(199244)	EN	15
R: CH DE ES FR GB IT LI					
JP 05506640	W	19930930	(199344)		8

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 510052	A1	WO 1990-SE886	19901228
		EP 1991-902229	19901228
JP 05506640	W	WO 1990-SE886	19901228
		JP 1991-502498	19901228

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 510052	A1	Based on	WO 9109627
JP 05506640	W	Based on	WO 9109627

PRIORITY APPLN. INFO: SE 1989-4407 19891229
AB WO 9109627 A UPAB: 19941115
The compsn. contains (1) an alpha-2-adrenergic agonist or other inhibitor of the sympathetic nervous system and (2) a natriuretic peptide, an ANP (Atrial Natriuretic Peptide) C-receptor ligand or neutral endopeptidase inhibitor. (1) is selected from methyldopa, **clonidine**, **guanabenz**, **guanfacine**, **idazoxan**, tolazoline, oxaminozoline, medetomidine, detomidine (MPV-253), bretylium, betanidine, debrisoquine, alpha-methyl-tyrosine or FLA-63.

(2) comprises the amino acid sequence Ser-Leu-Arg-Arg-Ser Cys-Phe-Gly-Gly-Arg Met-Asp-Arg-Ile-Gly Ala-Gln-Ser-Gly-Leu Gly-Cys-Ser-Phe-Arg-Tyr-COOH with a connecting double bond between the two Cys, or BNP (Brain Natriuretic Peptide), alternatively their pharmacologically active analogues, an ANP C-receptor ligand such as e.g.SC-46542, or inhibitors of the enzyme (Neutral Endo Peptidase - NEP 24.11;EC 3.4.24.11), primarily responsible for the degradation of ANP and BNP, the inhibitors in question being e.g. SCH 32615, SCH 344826, SCH

39370, SQ 290072, tiorfan and UK 69578.

USEangstromDVANTAGE - for treatment of heart failure and for increasing the pumping capacity of the heart with a synergistic effect. It is thought that the combination of a low dose of an alpha-2-adrenergic agonist and for example ANP will restore the normal diuretic and natriuretic response of for example ANP, otherwise lost in congestive heart failure. (Amended abstract)

3

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FILE 'HOME' ENTERED AT 14:22:37 ON 15 OCT 2001